MAJOR ENDOCRINE DISORDERS

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MAJOR ENDOCRINE DISORDERS

BY

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MAYO CLINIC U S A

FOREWORD TO FIRST EDITION
BY *THE LATE*

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FOREWORD TO THE FIRST EDITION

ADVANCES in endocrinology have been occurring so rapidly that it is indeed difficult for the busy medical practitioner to keep pace with them There are encyclopaedic works full of detail which however valuable for purposes of reference are on too large a scale for him to assimilate There are also books dealing purely with the physiology of the ductless glands necessarily cautious in tone which naturally do not include the therapeutical aspect There are others which are more frankly speculative

This is a condition of affairs which Dr Simpson has set himself to remedy He is already well known as an original worker and writer on the subject He has in my judgement succeeded in a really difficult task for within a comparatively small compass he has included all the important recent advances Where matters are still *sub judice* he has stated the arguments for and against and then expressed his own opinion where there is general agreement the reader is not left in doubt His statements are clear and precise and are largely the outcome of his own experience The profession at large should be grateful to him for providing such a useful and much needed book

W LANGDON BROWN

PREFACE

THE first edition of this book appeared in 1938 and was rapidly out of print The intervening war years have delayed the second edition Even now I am conscious of its imperfections in places A very great deal of it has been entirely rewritten to keep abreast of the numerous advances The rapidity with which endocrinology and its associated sciences advance makes it difficult to observe the rule that printer s proofs of the author s manuscript are only sent for minor alterations and the correction of inadvertent errors The first edition contained no references because the task seemed too formidable and the subject matter was mainly clinical from my own personal experience In the present edition I have endeavoured to give a sufficient number of representative references to permit those interested to trace the rest of the experimental and clinical literature

Since clinical endocrinology is more than ever dependent upon a sound knowledge of experimental endocrinology clinical descriptions are prefaced by separate sections dealing with the physiology of each endocrine gland However the clinical accounts are so written that they can be read independently of the experimental sections The book should therefore prove of value to the medical student the practitioner the consultant scientific workers in the ancillary sciences and those reading for the M D and M R C P examinations

I am indebted to Dr Bernice Tanner for kindly compiling the index and for looking through the final page proofs

I must add a note of appreciation to my secretary Miss F Gibbs who has dealt so efficiently and painstakingly with the whole manuscript

S LEONARD SIMPSON

January 1948

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INTRODUCTION

Since my fundamental approach to endocrinology has not changed since 1938 I have left the following introduction as it was in the first edition

Endocrinology is best approached from the solid background of general medicine of which it has now become an essential component Recent advances however call for an increasing knowledge and application of physiology and the extent of this dependency makes one wonder if the term *clinical* endocrinology will not become obsolete Pathology and histology will never cease to be of fundamental value and no theoretical considerations can ignore these important landmarks The history of endocrinology is both fascinating and instructive and for this reason even in this small volume I have ventured to include some historical details

Although the term polyglandular syndrome has been frequently used because of lack of knowledge the fact that we may now be able to diagnose the primary gland disorder should not blind us to the close interrelationship and reciprocal influence of all the endocrine glands Most of these receive trophic influences from the pituitary (Fig 1) and their removal leads to secondary changes in that gland The central nervous system and emotional centres are linked to the endocrine system via the important hypothalamic pituitary mechanism disorders or peculiarities of behaviour emotional reaction and even artistic talent may be associated with endocrine tendencies and sometimes with definite syndromes

Certain general considerations apply to most of the endocrine glands Thus apart from the single embryological adenoma adenomatous formation is often an expression of hyperplasia e g in the adrenal cortex secondary to the pituitary stimulation in acromegaly Small multiple adenomas are then usual but one of them may become so enlarged as to be the presenting feature (cf thyroid adenoma) Endocrine adenomas may be slow growing but may become malignant after many years A hyperactive endocrine tumour may cause atrophy of the corresponding gland(s) e g adrenal cortex or parathyroid and

removal of such a tumour may produce a temporary post operative insufficiency until compensating hyperplasia results (e g adrenal hypofunction or parathyroid tetany) and this may be

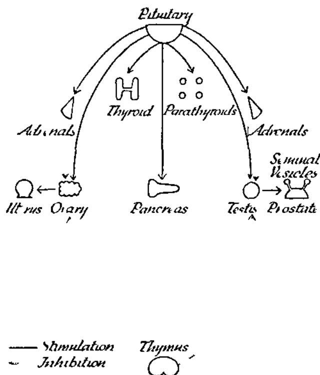


FIG 1 The main endocrine interrelationships illustrated diagrammatically For simplicity the reciprocal influence of other endocrine glands on the pituitary is omitted but removal of such glands e g thyroid or ovary leads to hyperplasia of the pituitary and to an increased secretion of its trophic hormones e g thyrotrophic gonadotrophic &c The adrenals are shown as inhibiting the gonads but in children sexual precocity may result from adrenal tumours Further elucidation of these and other complex reciprocal influences are discussed in the text

so severe as to result in post operative death unless substitution hormone therapy is given to tide the patient over this critical period

Endocrinopathies particularly of hyperfunction tend to occur spontaneously in waves of varying intensity irrespective

of therapy though should the patient survive hyperfunction may eventually give way to hypofunction e g myxoedema follow hyperthyroidism Infection has a considerable influence on the function of an endocrine gland usually impairing it e g diabetes mellitus but in some cases apparently augmenting it e g hyperthyroidism (unless it is assumed that the infection depresses another endocrine gland e g adrenal cortex which may normally inhibit the thyroid) The conception of dysfunction in endocrinology (e g dysthyroidism dysinsulinism) is tending to fall into disuse and most manifestations can be explained on a hyper or hypo secretory basis although these may occasionally alternate in waves

Endocrine disorders unless the term is limited to extreme and classical manifestations are by no means rarities In women the chances of the labile equilibrium of the endocrine glands being disturbed at puberty menstruation pregnancy and the climacteric are very considerable The constitutional background of the patient is even more important in endocrinology than in other branches of medicine Thus the results of castration or the climacteric which vary enormously in different individuals depend to a large extent on the endocrine constitution of the individual The reaction of the tissues to hormones which is variable is also important Thus although in one woman extreme hirsutism may appear to result from the excess of male androgenic hormone secreted by an adrenal tumour (and disappear after removal of the tumour) in another woman an equally severe degree of hirsutism may not be associated with a gross excess of androgenic hormone and further not all women with a considerable excess of androgenic hormone develop the same degree or distribution of hirsutism It may be that secondary sexual characteristics are not entirely dependent upon hormones since male and female excrete approximately equal amounts of both the male' androgenic hormone and oestrogenic hormone it is recognized however that excretion is not necessarily a measure of secretion Some forms of giantism are localized e g a leg or a toe whereas the amount of growth hormone is presumably equal at all sites of the body The reactivity of the tissues therefore is an important factor in determining the effects of hormone secretion

Although endocrine disorders may affect only one member of

a family it is not uncommon to find endocrine stigmata in others and giantism mild acromegaly puberty adiposity mild adreno genital syndromes and climacteric adiposity with diabetes and hypertension have all been found in one family Some endocrinopathies have a predilection for certain races e g adrenogenital syndrome in Celts and Hebrews giantism and acromegaly among Scandinavians and endocrine constitution may explain some racial characteristics When an endocrine disorder is constitutional it is as might be expected much more difficult to influence by therapy

It is important to realize that the signs and symptoms of endocrine disorders do not always conform exactly to those of the classical descriptions The present writer has frequently heard it argued that a patient cannot be suffering from Cushing s syndrome because there is no glycosuria or rarefaction of the bones or discoloration of the legs or that another cannot have Simmonds s cachexia because there is no bradycardia or severe wasting or that a normal blood pressure or serum sodium or absence of pigmentation excludes Addison s disease Undue reliance on classical descriptions inevitably leads to many errors of diagnosis Endocrine syndromes are rarely complete many departures from text book descriptions occur and they must be expected If endocrine manifestations are looked for with knowledgeable anticipation one becomes astonished at their frequency Endocrinology is a fascinating branch of medicine and any interest taken in it will not fail to be repaid for even granting serious limitations in therapy the number of undoubted therapeutic successes is sufficient to justify the study of the major endocrine disorders by the busy practising physician

SECTION ONE

THE PITUITARY

A PHYSIOLOGY

CHAPTER I

INTRODUCTION

Osler once said that if one really knew all about typhoid fever one would know the whole of medicine. An endocrinologist might well say: If one really knew all about the pituitary gland one would know the whole of endocrinology, because not only does the gland itself have important specific functions and not only does it influence most, if not all, the other endocrine glands, but the latter in their turn influence both the structure and functions of the pituitary gland. It is therefore appropriate that we spend some time considering its structure and physiological functions.

DEVELOPMENT

The pituitary gland (hypophysis) consists of an anterior lobe which is developed from a hollow upgrowth of the buccal epithelium and a posterior lobe which is derived from a downgrowth of the neural ectoderm of the third ventricle (hypophysis cerebri—outgrowth of the brain). This neural posterior part of the gland becomes the posterior pituitary or pars nervosa. It contains no nerve cells but is composed of neuroglial cells and fibres. It may be invaded by basophil cells or hyaline colloid cells. The stalk connexion between the floor of the third ventricle and the pars nervosa is called the infundibulum. The function of the pars nervosa and its relationship to the hypothalamus will be considered in the section on diabetes insipidus.

The anterior lobe consists of three portions: (1) pars anterior, (2) pars intermedia, and (3) pars tuberalis. The anterior and intermediate lobes are separated by a cleft, seen in the foetus and representing the hollow of the buccal upgrowth, and the intermediate lobe adjoins the posterior lobe. The pars tuberalis

is the fusion of two lateral outgrowths of the anterior lobe which spreads upwards around the infundibulum and beneath the tuber cinereum and which remains behind when the pituitary gland is removed This part of the gland is extremely vascular and consists in man of solid cords of non granular epithelial cells (Hewer 1941) The pars intermedia consists of clear cells occasionally granular arranged round vesicles which contain colloid It is histologically clearly marked off from the pars nervosa but merges into the pars anterior at the margin of the cleft (Hewer, 1941)

The pars anterior is the largest part of the pituitary and consists of columns of epithelial cells in a delicate vascular reticular network The cells are of three kinds (1) chromophobe which do not contain granules and do not stain with dyes (2) eosinophil or acidophil cells whose granules stain with acid dyes and (3) basophil cells whose granules stain with basic dyes The granules accumulate towards blood vessels indicating a secretory activity The acidophils and basophils are both called chromophils as distinct from chromophobes Since the cytoplasm of the chromophobe cells stains with difficulty or not at all a group of such cells has the appearance of a compact aggregate of nuclei In man the chromophobes constitute just over 50 per cent of the total cells the acidophils 35 per cent and the basophils 12 per cent (Rasmussen 1929) and this is similar to the proportion in the rat (Severinghaus 1933) The structure of the pituitary gland is however by no means static and the relative proportion of the three different types of cells varies physiologically e g during oestrous pregnancy climacteric after castration and in diseases such as acromegaly Cushing s syndrome and Addison s disease Some believe that the three types of cells merely represent different secretory stages of one cell types Others take the view that the chromophobe cell is a parent cell which can give rise either to acidophil or basophil cells Severinghaus (1933) showed that the Golgi apparatus which is a basket like network adjacent to the nucleus is different in acidophil and basophil cells and that some chromophobes by their characteristic Golgi apparatus are obviously pre acidophilic and others pre basophilic There is a good deal of evidence (see Acromegaly) that the acidophil (eosinophil) cells secrete the growth hormone and that the basophil cells secrete the gonadotrophic hormone (see discussion in Cushing s syn

drome) but since there are only three types of cells and a much larger number of functions performed by the anterior pituitary gland it is difficult to attribute these many other functions to specific cells and it seems theoretically certain that one type of cell must have multiple functions There is quite definite experimental and clinical evidence that the anterior pituitary secretes hormones which stimulate other endocrine glands to increased activity and such hormones are called trophic [1] (nourishing) hormones Thus we have thyrotrophic gonadotrophic adrenocorticotrophic and probably parathyrotrophic and pancreatotrophic (islet cells) In addition the anterior pituitary secretes the diabetogenic hormone These and other hormones possibly secreted by the pars anterior or pars intermedia will be discussed in the various sections of the book For clinical convenience the basophil cells will be considered in the Adrenal section since they are markedly reduced in number in Addison s disease (Crooke and Russell 1935) and may be relatively increased or form basophil adenomas or undergo vacuolization or hyalization in Cushing s syndrome (Crooke 1935) a clinical entity frequently associated with neoplasm or hyperplasia of the adrenal cortex

RESULTS OF HYPOPHYSECTOMY

Since destruction or removal of the posterior lobe has no effects other than the development of diabetes insipidus the results of total hypophysectomy must be ascribed to removal of the anterior lobe (including perhaps the pars intermedia)

Horsley Marianesco Gley and Galta were the early experimentalists in this field In 1910 at Johns Hopkins Hospital Cushing and colleagues performed hypophysectomy on dogs The results of complete hypophysectomy (Fig 2) were severe and ultimately fatal the longest survival period being 21 days The resulting syndrome termed cachexia hypophyseo priva was characterized by progressive weakness lethargy drowsiness anorexia hypothermia hypotension coma and death and corresponds to the clinical condition of Simmonds s cachexia

With incomplete hypophysectomy and probable incidental

[1] The term tropic is sometimes used meaning turning It is not really a shortened form of trophic but is a different word It is generally agreed that trophic is the better term

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FIG 3

FIG 4 EXPERIMENTAL ADIPOSITY AND INFANTILISM Produced in dog by partial removal of the anterior lobe of the pituitary interference with hypothalamus probable At autopsy pars nervosa not traceable and its site filled with pars intermedia cells Fatty infiltration of liver and myocardium ovaries infantile note slender extremities Front view shows control litter mate (Crowe S J Cushing H and Homans J (1910) *Bull Johns Hopkins Hospital* xxi 127)

trauma to the adjacent hypothalamus the post operative condition was less severe and the animals survived for some months or indefinitely They were still sleepy dull and inactive but in spite of a poor appetite they became very fat (Figs 3 and 4)

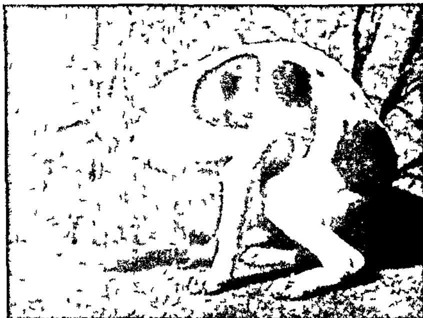


Fig 2 Showing cachexia and extreme weakness in fox terrier pup 3 days after complete hypophysectomy and a few hours before death (Ref Crowe S J Cushing H and Homans J (1910) *Johns Hopkins Hosp tal Bull* xxi 1 7)

although the extremities remained thin The growth rate was much diminished or ceased and the genitals remained infantile In fact the experimental picture corresponded to the classical picture of Frohlich s syndrome An additional feature which is not part of this latter syndrome was polyuria and this symptom indicates traumatic disturbance of the hypothalamic posterior pituitary mechanism The picture of profound adiposity combined with sexual atrophy was produced in the rat by Smith (1926) by injury to the tuber cinereum probably with involvement of the hypothalamus or by injection of chromic acid into the pituitary gland

The fundamental advance made by P E Smith working in the Department of Anatomy University of Columbia (1926

cavity beneath the pituitary and does not enter the buccal cavity. After trephining through the sphenoid and opening the dural sheath the ablation can be effected by means of a cannula and negative pressure. The dural capsule of the gland, except for the small ventral opening and the pituitary stalk, remains intact.

An almost complete growth stasis and a rapid regression in the size of the adrenals (involving chiefly cortex), the thyroids and sex apparatus, with accompanying structural modifications, result from the removal of the anterior and posterior lobes. This syndrome differs from that produced by injury to the tuber cinereum, the most pronounced feature of which is profound adiposity and a sexual atrophy. With posterior lobe ablation alone, the growth rate, sex apparatus, adrenals and thyroids are normal.

The Thyroid. Hypophysectomy invariably produced an atrophy or involution of the thyroid epithelium. In the controls the epithelium of all the follicles is of a cuboidal or low columnar type. In the hypophysectomised rat it is a squamous type and the nuclei are flattened. The colloid content is not markedly changed. There is a reduction in weight compared with the controls.

The Reproductive system. All my hypophysectomised rats have shown a pronounced retrogression and atrophy of all the reproductive organs. The ovary is greatly reduced in size. Atresia of the follicles sets in within a few days. Primordial follicles, however, continually are undergoing development, but invariably undergo atresia not later than the stage of cavity formation. The corpora lutea after hypophysectomy degenerate more slowly than they do in normal animals. The uterus and vagina atrophy. The testes of the operated rats are flabby and shapeless. The tubules are much diminished in size, and all indications of spermatogenesis are absent. Spermatogonia and degenerating spermatocytes are present, however, so that functional activity can be restored when the appropriate treatment is instituted. The interstitial cells exhibit no hypertrophy. The other portions of the reproductive tract show as great regressive changes as do the testes. At autopsy the testes are commonly found in the abdomen. The failure of the hypophysectomised male rat to exhibit any interest in a female in oestrus is in striking contrast to the behaviour of the gonadectomised male, for the latter will mate for some weeks after both testes have been removed. Sexual activity in the male clearly is dependent upon a hormone secreted by the pituitary as well as that elaborated by the testes.

The Adrenals. Ablation of the pituitary has invariably produced a pronounced atrophy of the adrenals. The small size of the adrenals is due not only to their failure to undergo further development following hypophysectomy, but also to an actual retrogression. The major decrease is in the cortex, but the medulla has not only failed to increase in amount following hypophysectomy, but has probably decreased slightly in amount. It is evident, however, that the retrogression of the cortex is almost entirely responsible for the decrease in weight of the adrenals following the ablation of the pituitary.

onwards) was however the development of a technique for performing complete hypophysectomy in the rat without disturbing the hypothalamus The result in essence was dwarfism,

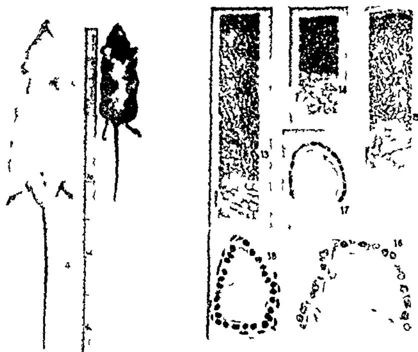


FIG 5 HYPOPHYSECTOMY *Left hand side* Hypophysectomized rat (with litter mate control) showing failure of growth after hypophysectomy at 26 days old (Photograph taken at 1[illegible] days old) *Right hand side* Nos 13 14 and 15 illustrate sections of adrenal cortex normal rat hypophysectomized rat hypophysectomized rat given pituitary transplant Nos 16 17 and 18 illustrate respectively sections of thyroid vesicle of normal rat hypophysectomized rat and hypophysectomized rat given anterior pituitary transplant By courtesy of Dr P E Smith (Ref *Amer J Anat* (1930) xlv [illegible] 20[illegible])

atrophy or failure of development of the gonads thyroid adrenal cortex and viscera loss of hair emaciation cachexia and death after some months—the autopsy findings being similar to those found in Simmonds s cachexia (Fig 5) The work is so fundamental that I quote the author s own account of his work

I have developed an approach to the hypophysis in the rat which permits the ablation of either the entire gland or only the posterior lobe without apparent brain injury This approach leads into the nasal

Crude extracts of the anterior pituitary prepared as growth hormone contain fractions of the other pituitary hormones e g adrenocorticotrophic and pancreatotrophic Evidence in favour of a specific action of growth hormone as well as the influence of other hormones on growth will be considered below

Extracts of the anterior pituitary gland also influence lactation (Prolactin) and breast development and function (Mammogen I and II) These will also be discussed in later sections

Since the pituitary gland contains only three types of cells only two of which are chromophil it is probable that one type of cell must secrete more than one hormone unless one postulates the secretion of a basic key hormone which becomes more specifically evolved according to the physiological (or pathological) needs of the organism at any one phase and dependent upon the activity or intervention of the other endocrine glands Our knowledge on this subject is as yet very incomplete

THE GROWTH HORMONE

(i) Introduction

The growth hormone was obtained from the anterior pituitary gland by Evans and Long in 1921 Experimental and clinical evidence indicates that it is secreted by the eosinophil cells It acts on the viscera and soft tissues as well as on bones but initial experimental work directed attention to its effect on the growth of long bones To appreciate this action and its clinical manifestations it is necessary to understand the essentials of the anatomy and physiology of bone development and growth

(ii) Anatomy and Physiology of Bone Development

Bone is a very highly specialized variety of connective tissue which is rendered rigid by the impregnation of its ground substance with calcium salts the skeleton contains about 97 per cent of the total calcium of the body From the point of view of development there are two kinds of bones (*a*) membranous (bones of the cranial vault) and (*b*) cartilaginous (long bones and most other bones) In both types embryonic connective tissue is transformed into bone by the activity of the specially modified fibroblasts known as osteoblasts but whereas with

Structurally the adrenal medulla shows no abnormality The cortex on the other hand exhibits a pronounced alteration The cells of all three zones exhibit a marked diminution in their cytoplasm The nuclei are constantly massed together It appears that the reduction of the cortex is not affected through disappearance of cells but rather by the diminution in their cytoplasmic content No zona fasciculata is distinguishable in the most atrophic glands delineation of the cells characteristic of this zone being absent Fat instead of being abundant in most of the cortex is limited to a narrow zone The retrogression of the cortex is rapid In six days the adrenals are but half the weight of the controls

Dwarfism The hypophysectomised rats exhibit an almost complete stoppage of skeletal growth This stoppage is immediate showing that there is little storage of the growth stimulating hormone of the pituitary

Growth and Epiphyseal closure The fact that the epiphyses remain open following hypophysectomy is not an abnormal condition in rats for these animals continue to grow through most of their life span and most of the epiphyses normally remain open until late in life

Simmonds s cachexia The rats operated on later in life (4 months) gradually developed a shaggy coat—and an emaciated or cachectic appearance—an appearance which did not develop in those operated upon at an early age The cachexia which developed in these older animals seems similar to the condition described by Simmonds There is lowered heat production lowered basal metabolism and a subnormal temperature

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THE HORMONES OF THE ANTERIOR PITUITARY

All the effects of hypophysectomy can be corrected by extracts of the anterior pituitary gland and the function(s) of separate chemical fractions will be considered in subsequent sections They are adrenocorticotrophic thyrotrophic gonadotrophic pancreatotrophic diabetogenic and probably parathyrotrophic All these stimulate other endocrine glands to activity Another hormone the growth hormone may or may not act without the intervention of other glands the question being undecided

from the anterior pituitary lobe of fresh glands of cattle contained a growth hormone. This emulsion, when injected daily, ½ to 1 c c intraperitoneally into young rats accelerated their skeletal growth rate compared with control animals and continued this growth for 200 days or more after that period in the life of an untreated rat when growth normally stops—about the 150th day of life. The rat is a suitable animal for testing growth hormone in so far as the epiphyses remain open until late in life. The hypophysis lobes were thrown into 40 per cent ethyl alcohol, agitated with a glass rod, transferred to two changes of sterile normal saline and triturated with force and speed with ocean sand, diluted with saline and decanted. The layers of sand, cell fragments and opaque pink fluid permitted the latter to be decanted. Later improved chemical methods permitted the preparations of alkaline extracts which contained the growth hormone in purer form. It is interesting and important to note that Evans (1923 4) recorded that success with parenteral dosage of mammals with beef anterior hypophysis was only obtained after failure in a long series of massive oral administrations. There is no doubt that in mammals the growth hormone is ineffective when given by mouth although this well established experimental fact is still ignored by some clinicians.

The effect of extracts containing pituitary growth hormone has also been dramatically demonstrated in hypophysectomized rats and in congenitally dwarfed mice.

Evans (1923) termed his normal rats injected with pituitary emulsions hypophysis giants and states that they were twice as heavy as the largest individuals known to us from our own and published records for this animal species. They were fat animals but a true overgrowth was participated in by the skeleton and by most of the viscera, especially the heart and lungs, liver, kidneys and alimentary tract, but not by the reproductive tract, the uterus and oviduct remaining infantile. He also observed that the growth and maturation of ova was impaired or prevented and postulated an antagonism between growth and sex stimulating hormone. Further observations suggested that corpora lutea were formed before ovulation occurred, and that his emulsions contained gonadotrophic luteinizing hormone.

membranous bone this is a direct process with cartilaginous bone there is an intermediate deposition of cartilage which acts as a temporary framework and is ultimately replaced by true bone In both instances the growth and changing shape of bones is a destructive as well as a constructive process The former which consists of the removal of the first formed bone is due to the activity of large multinucleated osteoclasts which originate from the same source as the osteoblasts and have the power of dissolving bone

A long bone is at one stage an homogeneous cartilaginous structure As such it can grow in any direction except that it is invested with a thickening of embryonic connective tissue which tends to maintain its shape This is called the investing perichondrium and at a later stage the periosteum At certain chronological stages (see Table) centres of ossification appear in the middle of the shaft (diaphysis) of the long bones and at either end (epiphysis) The process of ossification spreads from these centres outward and also from the periphery or circumference bone is laid down along the whole length of the shaft from the periosteal layer Ultimately the whole of the bone and of the two ends become completely ossified except for a line of cartilaginous cells which separates the shaft of the bone (diaphysis) from either end of the bone (epiphysis) This important layer of cartilage (epiphyseal plate) is the site at which growth takes place The cartilaginous cells proliferate but the layer remains narrow as the proximal older cartilaginous cells are replaced by osteoid tissue which becomes calcified Growth therefore takes place at both ends of each long bone At a certain age usually 16 to 18 the epiphyseal plate itself becomes replaced by bony tissue and the epiphysis is then said to be closed or to have joined the diaphysis At this stage growth is no longer possible In endocrine disorders closure of the epiphyses may be premature or delayed and even in apparently normal people there is considerable variation

(iii) The Discovery of a Growth Hormone

Although clinical and experimental evidence had previously indicated that skeletal growth depended upon the pituitary gland it was not until 1921 that Evans and Long at the University of California demonstrated that *a saline emulsion made*

Freud and others however working in Amsterdam in 1938 were able to prepare a highly purified preparation of growth hormone 'practically free' from other pituitary hormones but nevertheless highly potent in producing skeletal growth in rats. Earlier experiments also indicated that growth hormone was a specific entity. Thus Evans (1924) records that Smith and Allen showed that beef hypophysis is effective by mouth in hypophysectomized tadpoles in producing growth but that it does not produce metamorphosis or repair the atrophied adrenal cortex (interrenal) body or thyroid. Smith in 1930 demonstrated that whereas intramuscular transplantation of living pituitary glands from adult rats into dwarfed hypophysectomized rats restored the size and function of the thyroid, adrenals and gonads as well as producing growth, injections of a saline suspension of fresh gland affected growth only. We must therefore conclude that although extracts of growth hormone as usually prepared contain adrenotrophic and thyrotrophic hormones which have some effect on growth, there is a specific growth hormone which can be chemically separated and has a specific action. This is in keeping with the existence of clinical conditions in which the only defect appears to be that of growth hormone, although other clinical conditions confirm that the thyroid, the adrenal and the gonads themselves have an important influence on growth. Professor H. F. Evans and colleagues (1944) have recently shown that growth hormone produces skeletal growth and epiphyseal histological changes in the adrenalectomized hypophysectomized rat, clearly showing that its fundamental action is independent of the adrenal gland.

(vi) The Site and Mode of Action of Growth Hormone

Long bones are originally homogeneous cartilaginous structures, but from centres of ossification and from the periosteum bone is laid down until only a thin line of cartilaginous cells separates the shaft (diaphysis) from the end (epiphysis). This important layer of cartilage (epiphyseal plate) is the site at which growth takes place. The cartilaginous cells proliferate but the layer remains narrow as the proximal older cartilaginous cells are replaced by osteoid tissue which becomes calcified. At a certain age, e.g. 18, the epiphyseal plate becomes replaced by bony tissue and the epiphysis is then said to be

(iv) Congenital Dwarfism in Animals and the Significance of Eosinophil Cells

Smith and MacDowell (1930) studied a strain of black silver dwarf mice brought from England by Professor L C Dunn in 1928 and in whom the characteristic of dwarfism was shown by Snell to be a recessive Mendelian one These mice cease to grow after the end of the second week but although there is some delay in sexual development reproduction takes place The essential physiological defect is absence of the growth hormone and the essential histological defect in the pituitary gland of these animals is a complete absence of the eosinophil cells Implantation of the pituitary glands of these dwarf mice into immature female mice of a normal strain produces no acceleration of growth but accelerates sexual development The injection of growth hormone (see later) will produce growth in these dwarf mice Further experimental evidence to the effect that the eosinophil cells are the source of the growth hormone was provided by Smith who showed that the peripheral part of the bovine gland contains eosinophil cells and when stripped from the central basophil portion will yield growth hormone Clinically gigantism is associated with an eosinophil adenoma

It is also of interest to note that the thyroid and adrenal cortex of these animals are hypoplastic suggesting that the eosinophil cells are the source of the thyrotrophic and corticotrophic hormones

(v) Is there a Specific Growth Hormone?

Pituitary extracts containing growth hormone were found by earlier observers to contain also adrenotrophic and thyrotrophic hormones and prolactin Quite apart from the direct effect on skeletal growth shown by hormones of the adrenal cortex and thyroid (see later) and apparently by prolactin it is probable that these hormones have effects on metabolism which indirectly favour growth especially in hypophysectomized animals in which these glands are hypoplastic or atrophic Riddle and Bates (1938) suggested therefore that certain pituitary extracts owe their action upon growth to a balanced combination of prolactin thyrotrophic and adrenotrophic hormones rather than to a special growth hormone

does not develop beyond the skeletal age of 15 days even with pituitary growth extract unless thyroid is also given (Salmon 1941) Nevertheless if the rats are thyroidectomized at 35 days of age pituitary growth hormone will produce growth above normal rats even without additional thyroid although thyroid augments the effect In thyroidectomized hypophysectomized rats greatest growth is produced by pituitary growth hormone plus thyroid considerable growth by pituitary growth hormone alone but thyroid alone has no affect in the absence of the pituitary gland according to Evans Simpson and Pencharz (1939) Since thyroidectomy results in loss of the eosinophil cells from the pituitary gland the resulting stunting of growth would appear to be due to the diminished or absent secretion of growth hormone as well as to the diminished rate of metabolism

(viii) The Influence of Oestrogens and Androgens on Growth

Pre pubertal castration in man and animals shows that increased height may result from failure of the epiphyses to unite and continued action of growth hormone in adult life Conversely sexual precocity results in premature closure of the epiphyses and dwarfism Initially however sexual precocity is associated with an increased rate of skeletal growth and this is true in females and males Most normal boys continue to grow for some years after puberty and the epiphyses remain open during that time This is true of some girls but others cease to grow at puberty because the epiphyses of the long bones may close at that time

In some mammals e g dogs testosterone or oestradiol pro duce dwarfing by inducing premature union of the epiphyses but they also act by inhibiting the secretion of growth hormone by the pituitary gland if the doses used are sufficiently large In young boys with hypogonadism in which condition gonadotro phins which produce testosterone or testosterone itself may be indicated the hormone is usually administered with caution because of the theoretical possibility of premature union of the epiphyses but in actual practice in man this does not appear to occur and in fact skeletal growth appears to be appreciably accelerated In mice however both oestradiol and testo sterone inhibit the proliferation of cartilage and accelerate

closed or to have joined the diaphysis At this stage growth is no longer possible (Hewer 1941) Freud and colleagues (1939) found that the development of cartilage is gravely impaired by hypophysectomy and that growth hormone has a biologically typical point of attack at the proliferating cartilage' Ross and McLean (1940) observed that the administration of a growth preparation to rats that have reached a plateau of growth rate induces histological evidence of active growth in the quiescent epiphyseal cartilage and that this resumption of growth in the cartilage is often a better indicator of the activity of the preparation than an increase in body weight

The action of growth hormone depends to some extent on the reactivity of the tissues of the animal Thus in the bulldog there are changes in the skull bones and in the soft tissues comparable to those found in acromegaly whereas in the shepherd dog no such changes occur Growth hormone also produces in most species enlargement of all the viscera and especially of the liver, where the cells and cell nuclei undergo hypertrophy and in some cases central necrosis

Apart from bone and visceral changes important metabolic changes follow injection of growth hormone Lee and Schaffer (1935) found that even with paired feeding experiments (controls and injected rats receiving same amount of food) the injected rats gained more weight and retained nitrogen The gain in weight was due largely to water and to protein (83 per cent) while fat constituted only some 13 per cent whereas in the controls fat constituted 40 per cent This is a reversion to that found in rapidly growing animals Growth hormone also produces a fall in blood non protein nitrogen urea and amino acids and a fall in urine nitrogen (Long 1943)

(vii) The Effect of the Thyroid on Growth

In the strain of congenitally dwarfed mice (referred to above) thyroid alone produces a considerable amount of growth although not as much as pituitary growth hormone (Bates and others 1935) The rate of growth of young normal mice is consistently accelerated by thyroxine injected daily but the period of accelerated growth lasts for only 5 weeks after which time the control mice overtake the treated animals and the ultimate size is the same The skeleton of rats thyroidectomized at birth

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stopped Young therefore concluded that the growth activity as indicated by this nitrogen retention is closely related to the diabetogenic activity of a pituitary extract and that the mechanism of growth hormone activity consists of the induction of hyperfunction of the pancreatic islets and hypersecretion of insulin If a closer correlation with actual bone growth is demonstrable and especially if the latter can be induced by insulin action directly the theory put forward will prove attractive It seems justified even in the present incomplete state of knowledge to conclude that the pancreas like the adrenals and thyroid can be considered as capable of playing an important part in both experimentally induced or natural growth This is not going so far as to state that the growth hormone is identical with the pituitary pancreatotrophic hormone or diabetogenic complex

(x) The Standardization of Growth Hormone

Extracts of the anterior pituitary are usually assayed for growth hormone content by the increase in weight of normal rats after they have reached their plateau of growth and weight curve (150th day of life) or of hypophysectomized rats These methods are effective although fat and other tissues as well as skeletal growth play a part in weight increases Freud and others (1939) therefore used the hypophysectomized rat s tail as the test object The operation of hypophysectomy was carried out in 45 day old rats and their tail growth ceased unless growth hormone was subsequently injected whereas control rats tails grew 11 mm in 7 days and 25 mm in 21 days This method of assays was considered to be very accurate

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skeletal ageing (Silberberg 1941) Oestrogens also cause the deposition of calcium in the bones of mice the medulla becoming almost solid with bony spicules (Gardner and Pfeiffer 1943) and in fish and birds the blood calcium may rise considerably during maturation of the eggs or with injected oestrogens

(ix) The Role of Insulin in Growth Production

Growth is normally accompanied by nitrogen retention and Mirsky (1939) suggested that the nitrogen retaining action of anterior pituitary extracts is mediated in part by the islets of Langerhans of the pancreas Young (1944 1945) states that the growth hormone has not been separated from the pituitary diabetogenic hormone He further observed that in rats where the pituitary diabetogenic extract produces hypertrophy of islets of Langerhans but not diabetes growth is accompanied by nitrogen and water retention and by a catabolism of fat This is true in paired feeding experiments and also where the injected rats are permitted to indulge an increased appetite but in the latter experiments the loss of fat is not so great In both types of experiments the rats appear much fatter and better nourished than the uninjected controls but this is an illusion Analysis of the tissues showed 18 per cent protein 7 per cent fat and 60 per cent water &c in the injected rats compared with 16 per cent protein 15 per cent fat and 60 per cent water in the control rats Since the specific gravity of fat is less than unity while that of protein containing tissue with a substantial percentage of water is above one the injection of pituitary extract in Young's experiments led to a rise in specific gravity of the body mass and of its tissues Young quotes the work of Lee and Schaffer (1934) who showed that the tissues of pituitary treated intact rats contained less fat and more nitrogen than paired fed control animals The protein containing tissue is largely deposited in and around the abdomen

Puppies were found by Young to behave as rats but in older dogs increase in weight and growth usually stopped when diabetes developed Even so a positive nitrogen balance was often sustained in the presence of glycosuria and ketonuria and with a maximum D/N ratio When the animal became resistant to the pituitary diabetogenic extracts the positive nitrogen balance reverted to normal at the same time as the glycosuria

B CLINICAL

CHAPTER II

ACROMEGALY

Definition

ACROMEGALY is a condition due to a hypersecretion of the growth hormone and is characterized by enlargement of the hands and feet and of the bones and cutaneous tissues of the face and by splanchnomegaly &c

History

In 1886 Pierre Marie of the Salpetriere described two cases using the term acromegalie and quoting five cases with similar features from the literature In 1888 he collected further cases bringing the number up to seventeen However Sternberg (1897) recognized acromegaly in Wier s account of a giantess as far back as 1567 In 1932 Atkinson tabulated and analysed 1 319 cases with 265 autopsies

In his original paper Marie did not ascribe any cause to the disorder but in 1887 Minkowski connected the disease with the pituitary gland Benda (1900) was the first to detect an increase in the number of eosinophil cells in the anterior lobe of the pituitary this was confirmed by Lewis (1905) in a case in which there was no enlargement of the pituitary In 1895 Brissaud and Meige argued that giantism is acromegaly during the period of growth whereas acromegaly is giantism of the adult In 1921 Evans and Long produced giantism in rats by injection of anterior pituitary and in 1929 Putnam and others produced acromegalic changes in the head skeleton and viscera of English bulldogs

Pathology

The pituitary gland is usually although not necessarily enlarged and on section an eosinophil adenoma which may be microscopic in size or very extensive is found in the anterior lobe When the pituitary appears to be normal a differential

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some species pituitary diabetogenic hormone will produce hyperplasia of the islets before they degenerate The ovaries and testes are usually atrophic There is not much evidence on the histology of the ovaries although amenorrhoea is common but they may be cystic and degenerated free from follicles but rich in corpora atretica small and fibrous or multilocular cystic Cushing states that the mulberry ovaries (corpora lutea) of Evans's rats are not found in humans The testes are often soft and flabby the seminal vesicles disorganized and the interstitial cells degenerate The heart lungs liver spleen and kidneys are considerably enlarged the stomach is often double its normal capacity and both the small and large intestine are considerably increased in length and circumference Bony changes are considered in the clinical section

Physiology

The essential feature is the continued over secretion of growth hormone producing skeletal and visceral changes comparable to those of experimental acromegaly (see Physiological section) One can also postulate an excessive secretion of pituitary diabetogenic corticotrophic thyrotrophic and parathyrotrophic hormones and an inhibition of the secretion of gonadotrophic hormone

Incidence

Acromegaly occurs in all parts of the world and in all races Males and females are affected in equal proportions the incidence among Jews and Swedes being relatively high The maximum incidence is in the third decade of life It may however begin at puberty and Atkinson (1931) recorded one case at the age of 8 Childhood acromegaly is nevertheless a rarity If one includes relatively mild manifestations of the disorder acromegaly as most other endocrine disorders shows a family incidence in one series in 30 per cent of the cases Acromegaly is more likely to develop in tall people Thus Davidoff (1926) found in one series that the average height of men in whom the disease began before 20 was 6 ft 2 in and of women 5 ft 6 in

Aetiology

The cause of the development of an eosinophil hyperplasia or adenoma is rarely obvious Occasionally pregnancy or bilateral

cell count may nevertheless reveal a relative excess of eosinophil cells or there may be a local hyperplasia of acidophilic elements' (Cushing and Davidoff 1927) Occasionally a developmental pituitary nest of eosinophil cells is found at necropsy in the sphenoidal air sinuses (Erdheim) or as in one of Cushing s cases an enormous eosinophil adenoma projected outwards from the sella turcia leaving within an apparently normal pituitary gland Where there is a central eosinophil adenoma within the sella turcica the rest of the anterior lobe may be greatly shrunken and degenerate The pituitary gland may press on the optic chiasma eroding or invading the floor or roof of the sella turcica the cavernous sinus and the brain Cushing (1912) recorded a case of acromegaly in a man of 33 with two years history in which a large cerebellar cyst was the primary lesion this produced a secondary hydrocephalus which apparently resulted in an enlarged pituitary anterior lobe with hyperplasia of the eosinophil cells

The changes in the other endocrine glands are numerous and may be explained by oversecretion of the pituitary trophic hormones e g adrenal corticotrophic hormone by the eosinophil cells or by failure of secretion of trophic hormones e g gonadotrophic by encroachment of the eosinophil cells upon the basophil cells The pathological findings depend to some extent upon the phase of the disease over activity being followed by exhaustion of cells and under activity

The cortex of both adrenals is usually hyperplastic and multiple adenomas are frequently present The thyroid is enlarged in some 50 per cent of cases the usual change being an increase in vesicular colloid This is not easy to understand as thyrotrophic hormone experimentally produces hyperplasia of the vesicles (acini) which contain little or no colloid unless iodine is given at the same time A colloid goitre may be found in acromegaly even when complicated by thyrotoxicosis severe enough to call for thyroidectomy The parathyroids may be enlarged and adenomas have been recorded Enlargement of the thymus and diffuse lymphoid hyperplasia which also occurs both with Addison s disease and with adrenal cortical adenoma or hyperplasia are common The pancreas may be normal or atrophic or may show hyperplasia with perhaps adenomas of the islets of Langerhans This is explained by the fact that in

their termination giving the appearance of a podgy spade like hand but where skeletal overgrowth has occurred before epiphyseal fusion the fingers may be very long The long bones of the upper and lower limbs may show considerable periosteal thickening and deformity or may appear normal

The skull is considerably thickened the ridges becoming very prominent and the external occipital protuberance enlarged The cranial sutures may be obliterated Even more marked are the changes in the facial bones thickening and enlargement of the zygomatic arches of the malar bones and especially of the lower jaw which become prognathic through overgrowth and also through changes in the temporo mandibular joint The teeth become spaced wide apart as the jaw increases in width The clavicles are thickened and the antero posterior diameter of the chest is greatly increased The vertebrae undergo atrophy hypertrophy and partial fusion with resulting kyphosis lordosis and scoliosis A thickening of the ridge or bony prominence occurs where muscles or tendons are attached to bones and exostoses may appear near joints Arthritis may follow changes at the articular surfaces of bones and bony exostoses in the neighbourhood of the joints may severely limit movement Occasionally a portion of the skeleton such as one big toe appears to be more susceptible to the growth hormone and enlarges quite out of proportion to the rest of the skeleton This illustrates the principle that responsiveness of tissues as well as the concentration of the hormone stimulus determine the final result in endocrinopathies

Muscular system Hypertrophy of the muscular system associated with abnormal muscular strength may occur in the initial stages But though gigantic acromegalics may excel as wrestlers boxers or weight lifters their early prowess may be succeeded by muscular atrophy and atony

Soft tissues The tongue is greatly enlarged and the papillae prominent and in spite of the increased buccal cavity the tongue may be unable to find room within it and may interfere with articulation and tend to obstruct the air passages in the recumbent position The lips become thickened protuberant and negroid in appearance These changes in the lips and also in the nose may occasionally precede the skeletal changes

The skin and the subcutaneous tissue are thick the pores

ovariectomy may precipitate the disorder Although the highest incidence is in the third decade many patients have had some manifestations at puberty or in adolescence and it is probable that the physiological endocrine changes of this period may fail to be autonomously controlled or limited in those patients developing acromegaly The familial incidence in some 30 per cent of acromegalics suggests that this may be the case and apart from the occasional onset of the major disorder at puberty and in pregnancy transient fugitive acromegaly may occur at these periods It is not generally recognized that mild acromegaly is not infrequently found at the climacteric in certain types of women and men but it is a slow insidious process The onset in earlier life is also usually insidious and the disorder may progress for a decade or more before the patient realizes that he is suffering from a serious endocrine disturbance Occasionally general infection appears to be a precursor of the disorder e g measles typhoid

General picture As in many endocrine types there is a considerable resemblance among all acromegalics The large extremities awkward movements thickened features and drooping shoulders with hands falling near the knees in advanced cases give the picture of Simian man and where giantism has preceded the *acromegalic* changes of a primitive ape like giant Great strength however may give place to exhaustion and weakness in the later stages and in order to understand the symptomatology one must appreciate that over activity of the pituitary and related glands e g adrenals is followed by exhaustion and under activity and further that phases of activity may alternate with phases of inactivity before the terminal phase is reached

Skeletal changes As indicated by the name of the disease the more obvious changes occur in the hands and feet especially in the carpal and tarsal bones which are enlarged and may fuse The metacarpal and metatarsal bones are also thickened and the heads of the phalanges may show outgrowths or tufting on radiological examination The considerable and progressive increase in the size of the hands and feet which is due to the thickening of the soft tissues as well as to skeletal changes results in the characteristic need for an outsize in shoes and gloves The fingers are thickened and somewhat square in



Fig 6 (c) Same case showing enlargement of sella turcica and marked prognathism

Fig 6 (d) Same case showing tufting of the terminal phalanges

Fig 6 Acromegaly (a) Female acromegalic At age 0 (b) Same case age 4? showing coarsening of the features and the enlargement of the hands and feet gradual development

obliterated intervertebral foramina. Various types of chronic inflammation of the meninges of the skull and spinal cord, as well as of bony plates in the spinal dura, have been described. Areas of sclerosis may arise in the spinal cord with resulting ataxia and pseudotabes. True acromegaly may also be associated with syringomyelia, but this should not be confused with syringomyelitic bony deformities. Speech may be sluggish and slow, memory often being impaired, and the general behaviour characterized by apathy and lack of initiative. Depression, irritability, negativism, melancholia, mania, and delusional insanity may be additional symptoms. In the early stages or in relatively mild cases, however, there may be great alertness, energy, and drive.

The cerebrospinal pressure may be considerable, headaches being temporarily relieved by withdrawing some 10 c.c. of cerebrospinal fluid. In one case Simpson and Ellinger (1937) demonstrated an anti-diuretic hormone in the cerebrospinal fluid. This was associated with oliguria, positive water balance, and profuse sweating. Radiation of the pituitary gland produced a gradual disappearance of the anti-diuretic hormone from the cerebrospinal fluid, a concomitant disappearance of sweating, and a normal water balance. This case suggests that pressure or a nervous mechanism may produce over-activity of the pars nervosa, but in other phases of the disorder diabetes insipidus may be a complication through destruction of the pars nervosa by the encroaching eosinophil tumours.

Sexual system. Rarely an initial increase in libido may occur in both sexes, especially when acromegaly begins in adolescence. More commonly amenorrhoea and impotence are early features and are almost invariably present in the later stages. Nevertheless interference with sex function may not be obvious for ten or more years, though skeletal and other manifestations are progressive. Normal menstruation, pregnancy, and parturition occasionally take place when the acromegalic process is well advanced. In adolescent acromegalics the external genitals may be enlarged and puberty may be premature. In older acromegalics, however, impotence and amenorrhoea are often associated with atrophy of the genitals. The cause of initial sex stimulation in acromegalic adolescents may be ascribed to irritation of the basophil cells by the eosinophil tumour, whereas in

enlarged and the sebaceous and sudoriferous glands hypertrophied. Fibromata mollusca may be an expression of local hypertrophy of subcutaneous fibrous tissue. Excessive sweating (hyperidrosis) of the whole body may be troublesome and intractable and, together with the greasiness of the skin, results in persistent malodour. The hair on the trunk in both sexes may become abundant and coarse and wiry in character, the thick greasy hairy skin contrasting with the fine dry hair free (or covered with delicate hair) skin of the hypopituitary state. The enlargement of the hands and feet is partly that of soft tissue and the presence of associated tissue oedema is suggested by the diminution in size within a few hours following removal of a pituitary tumour.

Respiratory system. In both sexes the voice becomes deep and resonant, owing to the enlargement of the larynx and the increased width and resonance of the air sinuses, though the *mucous membrane may be so thickened that respiratory obstruction* may call for tracheotomy. Lungs are enlarged proportionately with the thorax. In the late asthenic stage of the disorder death may follow phthisis or broncho-pneumonia.

Cardiovascular. The heart may be enormously enlarged and all the coats of the peripheral blood vessels hypertrophied, hypertension being followed by hypotension in the later stages. Acrocyanosis and Raynaud's phenomena sometimes occur. Varicose veins are not uncommon, and superficial phlebitis or haemorrhoids may be superimposed.

Nervous system. Smell may be impaired owing to hypertrophy of the nasal turbinal bones. Pressure on the optic chiasma leads to optic atrophy, bitemporal hemianopia and later to complete blindness of one or both eyes. Ocular palsies may result from pressure on the third, fourth, or sixth nerves, and involvement of the fifth nerve may produce pain and hyperaesthesia over one or more of its divisions. Deafness may be due to involvement of the auditory nerve or middle ear.

Headache may be very severe and bursting in character. It is occasionally migrainous in type and associated with vomiting. Severe headaches are often quite intractable to medical therapy. Paraesthesias of the hands and legs may be early symptoms, though these disappear dramatically after operation. But true neuritis follows when somatic nerves are caught in

(a)

(b)

Fig 8 Acromegaly (a) The patient aged 25 before onset of the condition (b) The patient aged 30 Enlargement of the nose was the first complaint Hypertrophy of soft tissues Hand and feet and sella turcica enlarged

the later stages the basophil cells are encroached upon and destroyed

Carbohydrate metabolism Some 30 per cent of acromegalics have glycosuria and in about half of these the carbohydrate tolerance curves are indistinguishable from those of diabetics. Clinically a small percentage behave as such their tolerance progressively decreasing complications such as boils cataract and gangrene appear and death in coma may result. An adequate and normal response may be obtained with insulin but refractoriness also occurs. Most cases run a benign course and diet may have little influence though spontaneous recovery or even a supernormal carbohydrate tolerance may develop. The severity of the diabetes tends to follow the severity of the acromegalic waves diminishing or disappearing in remissions. Further removal of a pituitary eosinophil tumour may immediately abolish the diabetes while incomplete removal may accelerate the response to insulin. Hyperglycaemia may be succeeded by hypoglycaemia and increased tolerance if hyperpituitarism is followed by hypopituitarism. Associated with an increased carbohydrate tolerance may be a craving for sweet things. Polyuria and polyphagia may occur with or without diabetes.

Secretion of a diabetogenic hormone by the anterior pituitary has now been established and this hormone probably accounts for some cases of diabetes in middle age. It must certainly be a contributory if not a sole factor in producing carbohydrate disturbance in acromegaly. Young (see Pancreas section) has shown that the continued administration of diabetogenic hormone produces degeneration and atrophy of the islets of Langerhans (which changes are found in acromegaly) and to pituitary diabetes is thus added pancreatic diabetes. There is a further possibility that adrenal cortex hypertrophy may contribute to the diabetic manifestations. As regards the incidence of clinical diabetes Davidoff among 100 cases of acromegaly found 12 cases of classical diabetes and a further 13 cases of transient glycosuria. In the initial phases of experimental administration of pituitary diabetogenic hormone hypertrophy of the islets of Langerhans has been observed and this finding is also present in some cases of acromegaly. A separate pituitary pancreatotrophic hormone has also been postulated.

Manifestations of adrenal cortex hyperfunction In both sexes



(a)

(b)

Fig 9 Acromegaly with secondary virilism and goitre (a) The patient aged 0 and (b) aged 3 Note the thickening of the nose and lips prognathism hirsutism slight exophthalmos and thyroid enlargement Hands and feet enlarged at age of 3 virilism did not appear until 4 years later The sella turcica was considerably enlarged (For details see Ellinger Hare and Simpson *Quart J Med* 193, vi 241)

there may be extensive growth of coarse oily hair over the trunk. In the female abnormal hairiness sometimes develops on the face (Fig. 9) and extremities, and the hair of the head falls out as in primary adrenal virilism. Although adrenal cortex over-activity itself produces amenorrhoea, probably by inhibition of pituitary activity through excessive androgen secretion, it is unlikely to be the initial cause of amenorrhoea in acromegaly since amenorrhoea occurs early and often without any manifestations of virilism. Similar argument would also apply to impotence in the male.

The possibility of adrenal cortex hyperfunction being a factor in acromegalic diabetes has been mentioned in a previous section.

In the later phases of acromegaly, adrenal cortex hyperfunction may be followed by hypofunction, and Davidoff recorded pigmentation of the skin in 46 out of 100 patients.

Thyroid disturbances. Although the basal metabolic rate is increased in about 50 per cent. of acromegalics, a clinical picture of thyrotoxicosis is only found in some 5 per cent. In these as well as in other cases of acromegaly histological section shows a colloid goitre, which finding is rather difficult to harmonize with the hyperplasia produced by injected pituitary thyrotrophic hormone. Apart from thyrotoxicosis, the thyroid may be enlarged in some 20 per cent. of patients, and may produce pressure symptoms. Hypothyroidism is not infrequently present in the later asthenic phase of acromegaly and is associated with atrophy of the thyroid gland. Some degree of exophthalmos is not infrequent in acromegaly, even in the absence of hyperthyroidism, and must be attributed to the effect of thyrotrophic hormone, which experimentally can produce exophthalmos even in thyroidectomized animals.

Course and Prognosis

Acromegaly is usually a chronic progressive disease taking many years to develop. The changes may be sufficiently slow to last a lifetime without grave disability, though a patient can be completely incapacitated within a few years of the onset. Waves of remission and exacerbation occur in the more chronic types, and a stationary phase may last some years. The more active phase of the disease may ultimately be followed by an asthenic hypoactive phase in the same way as thyrotoxicosis

CHAPTER III

GIANTISM

Definition

GIANTISM is a condition of excessive height

Aetiology and Pathology

Giantism may be due to (1) an excessive secretion of the growth hormone before the epiphyses unite (2) to a delayed

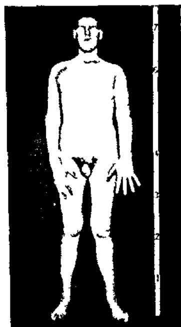


FIG 10 GIANTISM AND ACROMEGALY In a man of 21 Height 7 ft 6 in and still growing Slight enlargement of sella turcica but no eye changes incomplete sexual maturity and ununited epiphyses maximum strength at age 17 now declining Prognathism large hands and feet

union of the epiphyses (eunuchoidism) a normal amount of growth hormone thus being permitted to act over an abnormally long period and (3) to a combination of (1) and (2) An additional factor consisting of an inherent capacity of the bones

may after a variable course be ultimately followed by myxoedema even without surgical intervention

Treatment

Where there is involvement of cranial nerves especially the optic nerve surgical removal of the pituitary tumour is indicated The mortality is about 10 per cent and improvement takes place in some 70 per cent of cases In other cases a trial of X ray treatment is indicated and relief may be expected in some 50 per cent of cases Experimentally oestrogens and androgens inhibit pituitary activity and in the less severe cases it is reasonable to attempt to restrain the pituitary over activity by such hormones Cushing and Davidoff recorded that in one patient very large doses of anterior pituitary gland by mouth 100 grammes daily relieved severe headaches It is generally held however that anterior pituitary gland has no action when given orally

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Clinical Picture

Rapidity of growth is generally noted in childhood but may be most conspicuous during adolescence Acromegalic mani

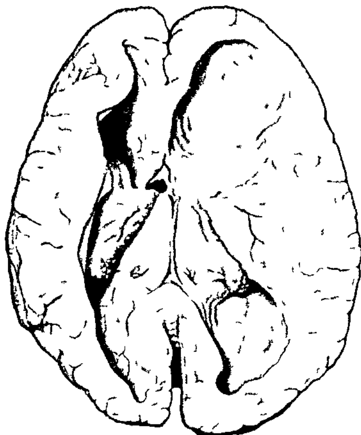


Fig 11 (b)

(b) Same case At operation and subsequent autopsy enormous dilatation of the lateral ventricles due to stenosis of the aqueduct of Sylvius by an astrocytoma section of the pituitary gland appeared to be normal

festations occur in some 40 per cent of giants and may be observed at puberty in adolescence or later in life

Sexual development and libido sexualis may be normal or even supernormal at first but after some years impotence may develop In the primary eunuchoid type hypogonadism is an

to respond to the stimulus of the growth hormone is probable Giantism tends to run in families and to be common among certain races e g the Swedish

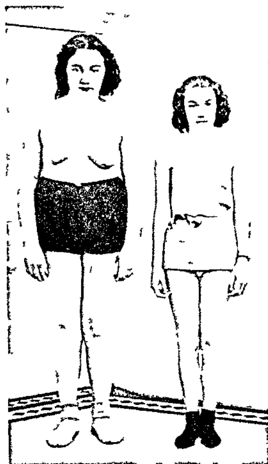
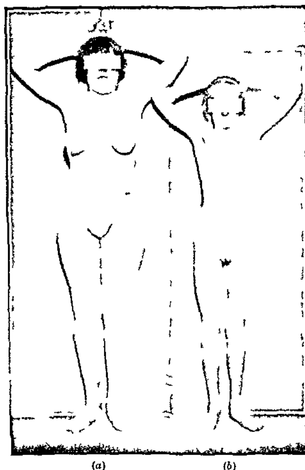


Fig 11 (a)

Fig 11 Giantism (a) Excessive growth (5 ft 11 in) and weight (2[illegible]0 lb) in a girl aged 14 (on left) with control girl of same age big hands and feet (size 9 men's shoes) no visual symptoms but papilloedema noted on examination of fundi

Macroscopically the pituitary gland may be normal or enlarged Microscopically it may not be possible to detect any abnormality or there may be a relative preponderance of or adenoma of eosinophil cells



(a) (b)

FIG 1. FACIAL GIANTISM SEXUAL DEVELOPMENT AND MODERATE ADIPOSITY (a) Patient aged 1? (Father a tall Swede) Normal childhood until the age of 3 Menstruation at 11 Note well developed breasts Shoes size 8 Gloves size 7½ (b) Control (rather thin) aged 1

initial and persistent feature the external genitals are small and the secondary sexual characteristics absent or deficient and there is delayed union of the epiphyses For this latter reason growth continues for some years longer than normal Further since castration results in over activity of the pituitary there may be with hypogonadism an excessive secretion of the growth hormone Excessive height is found among those Skopecs (a religious sect) who have been castrated before puberty The fundi are usually normal but in the presence of a pituitary eosinophil tumour optic atrophy may be observed with limitation of temporal fields of vision as in acromegaly In one patient (Fig 11) a girl aged 14 brought to Out Patients because of rapid growth (5 ft 11¼ in) and lack of energy (following on previous robust health) I was surprised to find bilateral papilloedema Ventriculogram (T G I James) showed symmetrical dilatation of the third ventricle and autopsy revealed a huge hydrocephalus resulting from complete stenosis of the aqueduct of Sylvius the lumen of which was completely obliterated by a subependymal gliosis Although the pituitary gland showed no obvious abnormality on histological section one must postulate excessive secretion of pituitary growth hormone (serial sections being cut) Other clinical features were plethoric countenance big hands and feet (men s size 9 shoes) slight adiposity but red lineae distensae of the abdomen and axillae no hirsutism and menstruation had not yet commenced The blood count and carbohydrate tolerance were normal

Occasionally in addition to the general giantism one part of the body—for example a leg or a toe—may grow to a greater extent than the rest Since the concentration of growth hormone is probably the same at all sites of the body one must postulate a localized tissue hypersensitivity the reason for which is as yet obscure Giants may show supernormal muscular power but after some years this may be followed by asthenia

Abnormal growth before puberty may occur, with tumours of the adrenal cortex the testis and the ovary and with other forms of sexual precocity but premature union of the epiphyses results in a final height below normal In the physiological section it has been noted that testosterone and oestradiol may produce excessive skeletal growth as long as the epiphyses remain ununited

characteristically by a strand or streak of epithelial tissue consisting of a primitive genital ridge composed only of stroma like cells and showing no proliferation or epithelium or

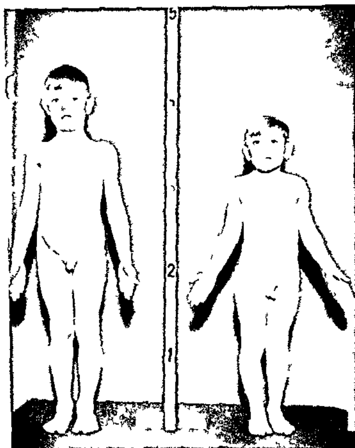


FIG 13 CONGENITAL DWARFISM Boy 8½ with control (on left) same age associated with congenital cardiac lesion Bone age 6 years As the mother is 4 ft 7 in and all her family short both the dwarfism and the heart lesion appear to be congenital and the latter only contributory to the dwarfism in the case

primordial germ cells In some patients it is arrested development rather than agenesis Albright Smith and Fraser (1942) state that

> The syndrome of primary ovarian insufficiency and decreased stature is characterised by infantile sex organs complete lack of breast development

CHAPTER IV

DWARFISM

THERE can be no absolute definition of dwarfism but if the height is obviously below the arbitrarily accepted lower level of normal limits dwarfism may be diagnosed If the condition is to be diagnosed before adult life the above definition must be qualified by the phrase as compared with individuals of the same age

Some of the causes of dwarfism are as follows

(1) *Genetic (uncomplicated)* In this group the only abnormality is a failure of skeletal growth presumably due to a congenital deficiency in the number of eosinophil cells (compare congenitally dwarfed mice—Pituitary Physiology section) This recessive gene may alternate with the contrasting one determining excessive height since it is not infrequent to meet exceptionally tall members of the same family

(2) *Precocious sexual maturity* This leads to a preliminary rapid skeletal growth but ultimate dwarfism because of premature union of the epiphyses This is well known in connexion with obvious pathological sexual precocity but it is less well recognized that many girls and some boys have premature union of the epiphyses of the long bones at the age of 14 or 15 instead of 17 to 18

(3) *Infantilism* q v

(4) *Babinski Frohlich syndrome* q v

(5) *Cretinism* q v

(6) *Eunuchoidism* The ultimate height in eunuchoidism is usually well above normal but in the childhood and early adolescent phase the height may be below average (see Eunuchoidism)

(7) *Associated with ovarian agenesis* This is a condition described by Albright Smith and Fraser (1942) Varney Kenyon and Koch (1942) and by Wilkins and Fleischmann (1944) and clinically might be mistaken for infantilism The fundamental distinguishing feature (apart from histology) is the high urinary gonadotrophic titres as compared with an absence of gonadotrophins in pituitary infantilism The ovary is represented if detectable by a very small immature organ or more

The primary genetic ovarian agenesis is not the cause of the dwarfism as in the primary gonadal failure of eunuchoidism without pituitary defect height is usually above normal A condition in males comparable to ovarian agenesis has not been described

(8) *Chronic illness in childhood* Syphilis tuberculosis malaria pancreatic disease including diabetes mellitus diabetes insipidus caeliac disease chronic diarrhoea (e g Crohn s disease) renal rickets and von Gierke s glycogen disorder &c are all causes of deficient growth with or without some failure of sexual development Malnutrition qualitative or quantitative is also a factor which operates in civilized communities and supplementary dietetic experiments in poor schools have demonstrated this in large numbers (Corry Mann 1926)

(9) *Achondroplasia* This is a congenital abnormality of cartilage bone formation arising in foetal life and characterized by short legs and arms a relatively long body good intelligence a big head and face a square nose with a depressed bridge and spade like hands Underlying endocrine defects have not been discovered These people breed families of achondroplasiacs They are active strong and acrobatic with normal intelligence and rather vain and are to be found on the stage and in circuses

(10) *Turner s syndrome* In 1938 Turner described seven girls from 15 to 23 years of age with heights varying between 48 to 55 inches who presented a syndrome of infantilism congenital webbed neck and cubitus valgus The breasts vagina and uterus were infantile and menstruation had not occurred A scanty growth of pubic and axillary hair was sometimes present Turner thought his cases corresponded to the Levi Loraine type of infantilism and that the anterior pituitary was at fault Wilkins and Fleischmann (1944) as well as Sharpey Schafer (1941) have indicated the similarity between ovarian agenesis and Turner s syndrome and Schneider and McCullagh (1943) in describing six additional cases of Turner s syndrome express the opinion that it is identical with ovarian agenesis A webbed neck is recorded in some 30 per cent of the cases of ovarian agenesis A wide carrying angle of the forearms or cubitus valgus is a feature of Turner s syndrome Apart from webbing of the neck the latter may be short and thick Other

small to moderate amounts of axillary and pubic hair in spite of complete absence of other so called secondary sex characteristics short stature the frequency of congenital anomalies especially webbing of the neck and coarctation of the aorta late union of the epiphyses often accompanied by epiphysitis osteoporosis precocious senility an excess of follicle stimulating hormone in the urine and a decrease but not an absence of the excretion of the 17 ketosteroids in the urine

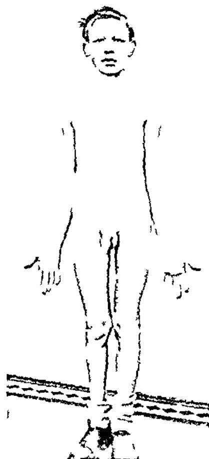


FIG 14 DWARFISM An unusual case of dwarfism (61 in) with hypogonadism and mental deficiency in an adolescent of 18 years X ray showed all the epiphyses ununited Although the penis and testicles were not undersized pubic axillary and facial hair were absent and the general appearance that of a boy The crooked little finger and primitive transverse creases of the palms are not infrequently associated with mental deficiency

They differentiate the condition from pituitary dwarfism (pan hypopituitarism) by the following criteria

A The individuals are short rather than dwarfs B The bone ages are only slightly retarded rather than markedly so C These patients have a reduced amount of axillary and pubic hair rather than none at all D Oestrin therapy in these individuals lead to marked increase in axillary and pubic hair whereas it has no such effect in pan hypopituitarism E These patients are quite strong and well nourished rather than weak and undernourished F The follicle stimulating hormone in the urine is increased above the normal rather than absent G The 17 ketosteroids in the urine are decreased but not minimal H In an insulin tolerance test these patients exhibit normal hypoglycaemia responsiveness as opposed to hypoglycaemia unresponsiveness I These patients are prone to have other congenital anomalies

Osteoporosis and hypertension may be features The failure of growth is ascribed to a genetic pituitary defect

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congenital defects may be present e g congenital heart coarctation of the aorta mental deficiency and absence of pigment in the retina and iris There are no abnormalities in the cervical

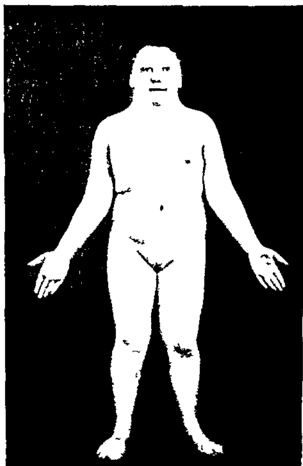


FIG 15 TURNER'S SYNDROME Woman aged 2 Dwarfism adiposity amenorrhoea and failure of sexual development are in keeping with the initial diagnosis of Frohlich's syndrome but the webbing of the neck and the wide cubital angle complete the Turner's syndrome 17 ketosteroids were only 2 6 mg per day fasting blood sugar 70 mg per 100 c c blood cholesterol exceptionally low 0 mg per 100 c c and repeated mg per 100 c c and the B M R unexpectedly high plus per cent

vertebrae as in the disorder described by Klipper Feil (synostosis of cervical vertebrae) Schneider and McCullagh state that the retardation of growth in Turner's syndrome becomes more

manifest at the age of puberty as the latter fails to occur They found an excess of gonadotrophins and moderately low 17 *ketosteroids in the urine*

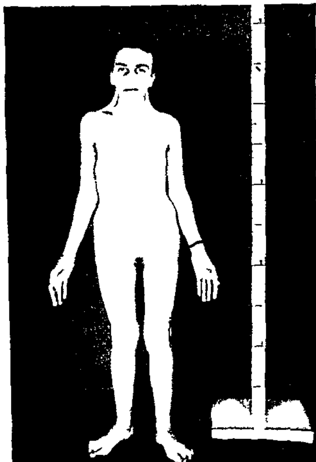


FIG 16 TURNER S SYNDROME Female aged 21 showing webbed neck infantilism and cubitus valgus at autopsy the ovaries were found to be destroyed by extensive tuberculosis but the pituitary thyroid and adrenal glands showed a normal histology (By courtesy of Dr E I Sharpey Schafer *Lancet* 8 Nov 1941 p)

The only autopsy recorded in a case of Turner s syndrome is that in a woman of 21 who died from miliary tuberculosis (Sharpey Schafer) The pituitary adrenal and thyroid glands were macroscopically and microscopically normal No functioning

ovarian tissue could be distinguished in the right ovary The endometrium was destroyed by tuberculosis The left ovary could not be found in the masses of tuberculous granulation tissue Apart from the features of the syndrome the patient was in good health until a few months before death when abdominal tuberculosis made itself manifest

Diagnosis

In uncomplicated cases this is merely dependent upon the height of the individual It is obvious that many short people are otherwise perfectly formed and some occupy very eminent positions The intellect may be normal or well above normal As part of a syndrome the differential diagnosis is indicated in the clinical section

Treatment

Any underlying disease or causative lesion calls for its appropriate treatment No treatment is of avail if the epiphyses are united or if the patient's chronological age is much above that of adolescence Pituitary growth hormone (see Infantilism) is theoretically specific but available preparations are on the whole disappointing Thyroid by mouth is sometimes helpful quite apart from cretinism The treatment of the various endocrinopathies of which dwarfism is a feature is discussed under separate headings

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CHAPTER V

INFANTILISM

Nomenclature and Definition

INFANTILISM is a condition of somatic growth and sexual development corresponding to a normal individual several years younger than the patient and never attaining adult physique or sexual maturity The term Levi Loraine syndrome is used synonymously with infantilism Actually Loraine wrote a preface to a paper by one of his pupils Faneau de la Cour who submitted his thesis in Paris in 1871 under the title La Feminisme et l infantilisme chez les tuberculeux Failure of somatic and sexual development was thus observed as a result of chronic tuberculosis of various types commencing in childhood Ettore Lévi (1908) described several cases of infantilism and in particular its occurrence in two sisters aged 15 and 20 in the elder of whom there was enlargement of the pituitary fossa and optic atrophy He thus drew attention to a pituitary type of infantilism although his account appears to envisage a polyglandular disturbance He also described infantilism as secondary to rheumatic carditis in childhood One of the important diagnostic features stressed by Levi was the ununited epiphyses which we now know as a manifestation of any type of hypogonadism

Brissaud described a thyroid type of infantilism which is more correctly spoken of as cretinism or if commencing in childhood as juvenile myxoedema However one occasionally meets with a type of pituitary infantilism complicated by clinical signs of hypothyroidism and then the term Brissaud s syndrome might be applicable

Frohlich s syndrome is by our previous definition a form of infantilism but since infantilism is usually applied only to those patients who are not fat and who are usually thin and since Frohlich s syndrome is said to have connotation of fatness as an essential feature this disorder is described separately Another atypical type of infantilism associated with a primary ovarian defect will be considered under a separate heading

ovarian tissue could be distinguished in the right ovary The endometrium was destroyed by tuberculosis The left ovary could not be found in the masses of tuberculous granulation tissue Apart from the features of the syndrome the patient was in good health until a few months before death when abdominal tuberculosis made itself manifest

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Pathology

Unfortunately there is little or no evidence of the pathology or morbid anatomy of uncomplicated infantilism Craniopharyngioma may produce infantilism but complicated by other secondary endocrine disturbances (Rowlands and Simpson 1942)

Clinical Description

Apart from retarded skeletal growth and sex development patients with infantilism usually present a delicate and gracious appearance They are pleasing to the eye and in no sense whatsoever grotesque Their childlike and often attractive appearance compels friendship and sympathy and a desire to help and protect them Their physique is on slender and graceful lines with narrow shoulders and narrow hips slender tapering fingers often relatively and somewhat surprisingly long and slender and well shaped legs The skin is of smooth and delicate texture and the complexion good In males the penis and testes remain infantile and there is an absence of sexual hair on the face and body Rarely pubic and axillary hair is represented by a small growth but the pubic hair never extends on to the abdomen in male triangular fashion The voice does not break



FIG 18 IDIOPATHIC INFANTILISM Boy aged 16 no sign of puberty bone age 1[illegible] years

In females there is amenorrhoea the uterus is infantile the breasts do not develop and the pelvis does not become wide at puberty

Intellect is in no sense impaired although the emotional and behaviour pattern often retains childish characteristics Some

Dwarfism is a failure of one function only namely skeletal growth and may be present with normal sexual development The term is therefore not synonymous with infantilism

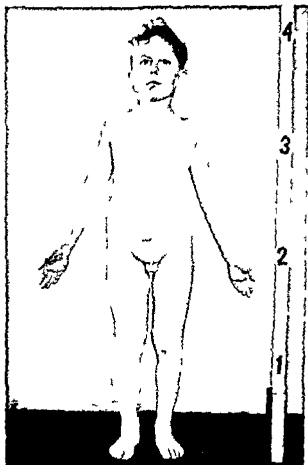


Fig 17 Lévi Loraine Infantilism (Patient referred by Mr Warwick Bailey) Aged 16 height 3 ft 10 in father and brother 6 ft mother ft 3 in weight 11 lb at birth epiphyses ununited infantile penis and testes no pubic hair baby face pituitary fossa extremely small no appreciable response to pituitary growth hormone

Progeria (premature ageing) is the term applied by Hastings Gilford (1902) to signs of senility superimposed upon infantilism in childhood or adolescence It is discussed in the differential diagnosis of Simmonds's cachexia

contrary to our definition may not be conspicuously impaired In the male the penis and testes tend to be subnormal in size and the pubic hair horizontal the voice is rather high pitched the skin of delicate feminine texture and facial hair slight in amount so that shaving every other day may be sufficient However such patients may be fertile In the female the pelvis remains narrow and the breasts small menstruation is often scanty but conception may occur These varieties of incomplete infantilism have their parallel in strains of dwarfed mice in which failure of somatic growth and incomplete sexual development are genetic disturbances associated with pituitary defects (see Physiology of Pituitary)

Clinical Types

(1) *Pituitary infantilism* Clinical or radiological evidence of a pituitary defect is a rarity but cases occur from time to time Wilkins and Fleischmann (1944) report with photograph a typical case in a girl of 21 due to suprasellar cyst

(2) *Idiopathic infantilism* This is the largest group but by comparison with the known cases of pituitary origin and because of our physiological knowledge a pituitary aetiology by inference is justifiable It is confirmed by the response of the gonads more especially in males to pituitary or chorionic gonadotrophic hormone

(3) *Hypothalmic infantilism* I have met with several cases of arrested development following severe shock or concussion or a severe virus disease such as measles complicated by encephalitic symptoms It would appear that in all these cases a hypothalamic pituitary mechanism is inhibited or brought into play

(4) *Chronic infection* This includes the tuberculous group of de la Cour and Loraine The tuberculosis can be bone glandular abdominal or pulmonary but must have continued in a chronic form during several years of childhood The French writers also postulate congenital syphilis as a cause Chronic malaria in childhood and in fact any chronic infection may be aetiological The mechanism is not understood

(5) *Chronic diarrhoea* Any cause of chronic diarrhoea in childhood e g coeliac disease pancreatic disease ulcerative colitis and Crohn s disease (Snapper 1937) may result in

people with infantilism especially incomplete forms attain intellectual brilliance and high scientific and cultural distinction

As in nearly all endocrine disorders an incomplete form of



Fig 19 Infantilism Boy aged 16 infantilism associated with hypospadias and left sided cryptorchidism right testicle just palpable outside inguinal canal no response to gonadotrophin inguinal operation some years ago unsuccessful Note cubitus valgus (as in ovarian agenesis)

infantilism must be recognized especially as it is probably much more common than the classical complete type With partial infantilism the general and somatic descriptions given above are usually applicable but hypogonadism is not complete and

but not to an extent that results in closure of the epiphyses It is usually ineffective in the female Testosterone or methyl testosterone may be helpful in both sexes appearing to produce somatic growth and muscular development However some patients seem to be fundamentally refractory to all treatment

REFERENCES INFANTILISM

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infantilism Poor absorption of food appears to be the most important fact and chronic inanition may also result in failure of development

(6) *Metabolic disorders* Severe diabetes mellitus diabetes insipidus von Gierke s glycogen disorder and renal rickets in childhood may also produce infantilism Diabetes mellitus however may develop some years after infantilism is well recognized and it is postulated that this might be due to a lack of the pituitary pancreatotrophic hormone (Gibson and Fowler 1936)

(7) *Cardiac disease* Congenital heart disease and severe rheumatic carditis in childhood may result in infantilism

Diagnosis

This depends upon the essential features of subnormal growth infantile genitals absence of secondary sexual characteristics long delayed union of epiphyses paucity of fat and slender build

Eunuchoidism may simulate infantilism in childhood or early adolescence (Simpson 1946) but with continual observation the ultimate height is seen to be above normal in eunuchoidism and below normal in infantilism Further eunuchoidism fails to respond to gonadotrophic hormone

Primary ovarian agenesis associated with dwarfism is difficult to differentiate from pituitary infantilism and ultimately it is a question of definition But with ovarian agenesis pubic and axillary hair is often present in some degree and the epiphyses are not infrequently partially fused As in all primary gonadal defects or insufficiency the urine shows an excess of gonadotrophic hormone whereas in pituitary infantilism no gonadotrophic hormone can be demonstrated in the urine

Frohlich s syndrome is distinguished from classical infantilism by the presence of some adiposity and by the tendency to a gynaecoid pelvis in both sexes

Treatment

The endocrine treatment of infantilism may be disappointing My own results from pituitary growth hormone are not decisive Thyroid is hardly called for in the absence of a thyroid deficiency and yet it often appears to result in increased growth Gonadotrophic hormone tends to produce sexual maturity in the male

but not to an extent that results in closure of the epiphyses It is usually ineffective in the female Testosterone or methyl testosterone may be helpful in both sexes appearing to produce somatic growth and muscular development However some patients seem to be fundamentally refractory to all treatment

REFERENCES INFANTILISM

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WILKINS L and FLEISCHMANN W (1944) *J Clin End* iv 306

CHAPTER XI

BABINSKI FROHLICH SYNDROME

(Frohlich s Syndrome Adiposo genital Dystrophy)

History

In June 1900 Joseph Babinski the famous French neurologist and pupil of Charcot presented to the Societe de Neurologie de Paris a paper with illustrations of a girl aged 17 years with failure of sexual development and obesity apparently due to a craniopharyngioma (as judged by autopsy descriptions) The title of this paper was Tumour of the Pituitary Gland without Acromegaly and with arrest of Development of the Genital Organs *In the following year Alfred Frohlich of Vienna* described a similar case due to a craniopharyngioma in a boy of 14 years under the heading A Case of Tumour of the Hypophysis without Acromegaly and owing to historical researches into probable cases described in the preceding fifty years and fuller description the disorder is usually called after him The French adhere to Babinski s name and the Germans call it Frohlich–Babinski s syndrome (Rolleston) The descriptive label adiposo genital dystrophy was introduced by Bartels in 1908

Definition

Owing to a number of conditions allied to and confused with this syndrome it is important to lay down a definition which is quite clear if to some extent arbitrary The following definition is suggested A syndrome characterized by a failure of normal *maturation of the gonads and by adiposity and due to a primary* hypothalamic hypothalmic pituitary or pituitary lesion Sub normal skeletal growth (dwarfism) and diabetes insipidus are other features which may be present but which are not essential for the diagnosis

Pathology

According to Kraus (1945) the following lesions have been known to cause the adiposo genital syndrome craniopharyn

glioma (intrasella or suprasellar) chromophobe adenoma third ventricle tumours chronic hydrocephalus chronic tuberculous or syphilitic meningo encephalitis epidemic encephalitis and meningo encephalitis bullet wounds fracture of the skull &c He further states that in cases of severe and long standing hydrocephalus the hypophysis shows depletion of the chromophilic cells and finally atrophy of the whole organ However the hypothalamic pituitary cause of the syndrome is more often a matter of inference based on experimental knowledge rather than one of histological demonstration Unfortunately the known pathology of the allied Laurence–Moon Biedl syndrome (q v) does not add appreciably to our knowledge of the pathology of Fröhlich s syndrome

Incidence

The adiposo-genital syndrome associated with a gross pathological lesion is very rare A true adiposo genital syndrome justified by clinical criteria and without a gross pathological lesion, is also in my experience a rarity Conditions which may be confused with it are common and will be discussed

Clinical Picture

Failure of sexual maturation is an essential feature As proper maturity in normal subjects does not occur before puberty the sexual factor can only have a relative significance before puberty in the male and even less in the female In the boy it may be possible to state from appearances that the penis and gonads are retarded in their development and subnormal in size At the time of normal puberty and with greater certainty in adolescence it will become clear that the penis and testes retain infantile or childish proportions and no secondary sexual characteristics develop Pubic and axillary hair does not develop and the face is free from any sign of male hair In the female menstruation does not occur

Frohlich s description included the following paragraph

> The penis which is otherwise (*ubrigens*) normally developed appears to be embedded in accumulations of fat to such an extent that the genitals approach the female type The testes are palpable in the depth of the fatty tissue and show infantile condition (*Verhaltnisse*) In the neighbourhood of the breasts there are also considerable accumulations of fat In the mammary glands several nodules are palpable but fluid

BABINSKI-FROHLICH SYNDROME

(Frohlich s Syndrome Adiposo genital Dystrophy)

History

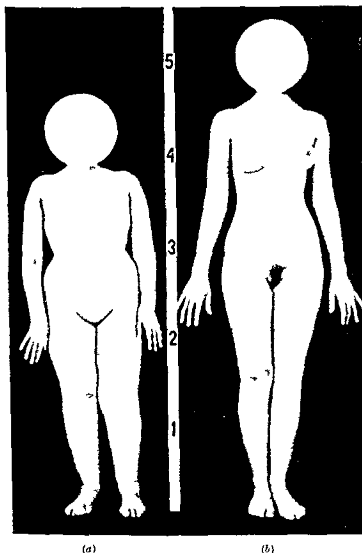
IN June 1900 Joseph Babinski the famous French neurologist and pupil of Charcot presented to the Societe de Neurologie de Paris a paper with illustrations of a girl aged 17 years with failure of sexual development and obesity apparently due to a craniopharyngioma (as judged by autopsy descriptions) The title of this paper was Tumour of the Pituitary Gland without Acromegaly and with arrest of Development of the Genital Organs In the following year Alfred Frohlich of Vienna described a similar case due to a craniopharyngioma in a boy of 14 years under the heading A Case of Tumour of the Hypophysis without Acromegaly and owing to historical researches into probable cases described in the preceding fifty years and fuller description the di order is usually called after him The French adhere to Babinski s name and the Germans call it Frohlich–Babinski s syndrome (Rolleston) The descriptive label adiposo genital dystrophy was introduced by Bartels in 1908

Definition

Owing to a number of conditions allied to and confused with this syndrome it is important to lay down a definition which is quite clear if to some extent arbitrary The following definition is suggested A syndrome characterized by a failure of normal maturation of the gonads and by adiposity and due to a primary hypothalamic hypothalmic pituitary or pituitary lesion Sub normal skeletal growth (dwarfism) and diabetes insipidus are other features which may be present but which are not essential for the diagnosis

Pathology

According to Kraus (1945) the following lesions have been known to cause the adiposo genital syndrome craniopharyn



(a) (b)

FIG 0 FRÖHLICH'S SYNDROME (a) The patient aged 19 dwarfism, adiposity amenorrhoea infantile uterus no secondary sexual characteristics Deficiency of growth hormone is not necessarily a characteristic of this syndrome (b) Control aged 19

cannot be expressed Hairs in the axillae are lacking and only occasional small hairs are present in the genital region There is at least a suspicion of a myxoedematous condition

The cause of hypogonadism is failure of the pituitary gonadotrophic secretion even when the initial lesion is hypothalamic because apart from morbid anatomy (1) patients (at least males) respond to a gonadotrophic stimulus and (2) biological assays *show an absence of gonadotrophic hormone in the urine (Nathanson and Aub 1943)* The cause of adiposity in Frohlich s syndrome will be discussed under the Adiposity section but it is probably hypothalamic in origin as is indicated by the work of Bailey and Brewer (1921) Especially is this likely to be the case when diabetes insipidus is a complication Contrary to general opinion the adiposity in the original cases of Babinski and Frohlich was only moderate in amount and it is doubtful if adiposity of marked degree is a feature of the syndrome However the distribution is characteristic namely face and neck breasts abdomen pubis and thighs It is usually stated that the distal limbs are thin and graceful This is not always so as illustrated in one of my cases (Fig 20) Bluish red mottling of the skin occurs on the outer thighs and over the buttock area Abdominal lineae distensae are white and not red The general *appearance of the male patients is feminine and the pelvis is* gynaecoid Drowsiness polyuria and polydipsia when present are regarded as hypothalamic symptoms Very little is known of the metabolism and biochemistry of the adiposo genital syndrome and the significance of such studies as have been made (Werner 1941) depends upon the criteria of diagnosis A craving for sweet things may be present and associated with a tendency to hypoglycaemia

Dwarfism or subnormal height constitutes the triad of the adiposo genital syndrome and always permits a diagnosis with greater confidence In my opinion a height above normal rules out this condition Ununited epiphyses are a manifestation of hypogonadism *The muscles tend to be hypotonic and hyper* extensibility of joints may be noted

Diagnosis

This depends essentially upon definition and should not be made with any dogmatism before puberty Hypogonadism

(3) *Adipose gynandrism* This is the name suggested for a syndrome that is very frequently met with and which is described sporadically in various degrees of incompleteness but has not been crystallized as a separate entity It will be described under a main heading but is characterized by a delayed but spontaneous evolution of sexual maturity associated with adiposity but with a gynaecoid pelvis and feminine genital hair and facies in the male

(4) *Infantilism* This should not be confused with the Babinski Fröhlich syndrome if it is appreciated that by definition infantilism cannot be associated with adiposity

(5) *Laurence–Moon–Biedl syndrome* This disorder (which see) is characterized by adiposity hypogonadism polydactylism mental deficiency and retinitis pigmentosa It tends to occur in families

Prognosis

Both Babinski s and Fröhlich s patients with craniopharyngiomas died in the second decade In the absence of a gross lesion survival is the rule Adiposity is refractory

Treatment

Any local intra cerebral condition calls for appropriate surgical treatment Adiposity receives the general treatment of this condition (which see) Gonadotrophic hormone is effective in the male and less so in the female Testosterone is a useful adjunct

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adiposity and dwarfism after puberty make a diagnosis very probable but the latter is not an essential feature The following conditions should be differentiated

(1) *Constitutional familial adiposity* In this condition the genital development is normal or slightly retarded In boys the

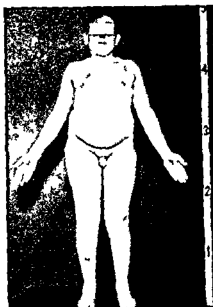


Fig 21 Fröhlich's Syndrome Male aged 23 height 4 ft 11 in weight 10 st 12 lb small but not infantile genital very few pubic and axillary hairs no hair on face no shaving voice not broken all epiphyses still ununited

penis is often embedded in the pubic fat and therefore appears smaller than it is This condition is frequently diagnosed as Fröhlich's syndrome In the absence of pathological knowledge one can only theorize as to conditions intermediate between this and Fröhlich's syndromes Fröhlich himself referred to the masking effect of the suprapubic fat on the size of the penis in his own patient so that this in itself obviously does not exclude the diagnosis

(2) *Cushing's syndrome* If this occurs at or before puberty sexual development may be delayed The facies is congested or plethoric and the lineae distensae are red or violet rather than white

was atrophic The pituitary and pineal bodies and the brain were macroscopically normal In the testes there was no evidence of maturation of spermatozoa and the interstitial cells were decreased in number Microscopically the adrenals parathyroids and pancreas gland were apparently normal The thyroid contained many dilated acini filled with colloid and lined with cuboidal epithelium and was considered to be a typical colloid goitre The pituitary was histologically remarkable The anterior lobe was composed chiefly of basophilic and eosinophilic cells The marked predominance of the basophilic cells coloured the sections blue to the naked eye In serial sections no adenomata were seen Differential counts showed 42 per cent basophilic 36 per cent eosinophilic and 22 per cent chromophobe cells as compared with the normal 11 37 and 52 per cent respectively There was no evidence of any hyaline change in the basophil cells In the pars intermedia no colloid was seen however there was moderate invasion of the posterior lobe by basophilic cells No definite changes were found in the hypothalamus or brain microscopically except for diminution of Perkinje cells and loss of nerve cells in the granular layer of the cerebellum Anderson (1941) believes the significance of a preponderance of basophil cells in his and Griffith s cases may be significant In both however there was chronic kidney disease and in one severe hypertension which Cushing has associated with basophilia I doubt whether the autopsies on patients with the Laurence Moon Biedl syndrome have as yet elucidated the aetiology of this condition or the allied one of adiposo genital dystrophy The former condition is probably not a primary endocrine disorder

Incidence

Cockayne Krestin and Sorsby (1935) record that during the period 1925–35 thirty isolated cases had been reported in addition to fifteen familial groups

Clinical Picture

A characteristic case suffers from mental defectiveness polydactyly pigmentary degeneration of the retina (retinitis pigmentosa) adiposity and hypogenitalism Adiposity is nearly always constant but of two brothers with the disorder one was

CHAPTER VII

LAURENCE MOON BIEDL SYNDROME

Definition

A SYNDROME occurring sporadically and in families as an autosomal recessive and characterized by polydactyly mental retardation retinitis pigmentosa with hypogonadism and adiposity and relative dwarfism being present in some if not all members of the family affected

History

Laurence and Moon first described the condition in the *London Ophthalmic Review* of 1866 Four of ten children of non consanguineous parents were affected It is recorded that one of the adults affected measured only 54 inches Sievert and von Jalsch noted optic atrophy associated with the condition and realized the possible relationship with Frohlich s syndrome but it was Bardet (1920) and Biedl (1922) who postulated this connexion more clearly Professor Sorsby (1935) to whom we owe a great deal of modern knowledge of the disorder although his original approach was as an ophthalmologist suggests that Bardet s name should be linked with Laurence and Moon s

Pathology

No autopsy had been recorded until 1936 and since that time 4 fairly complete and 2 incomplete autopsies have been described and are summarized by Anderson (1941) In the first autopsy the pituitary was apparently normal in the second the sella turcica was enlarged and occupied by a large cyst only a small portion of the glandular tissue remaining in the third (Griffiths 1938) there was a strikingly high proportion of basophilic cells and a relative paucity of eosinophil cells in the pituitary in the fourth and fifth cases (Riggs) two males of 19 and 24 infantile testes were present and certain changes were noted in the brain but not in the hypothalamus or pituitary Anderson s case was a 15 year old boy who died with uraemia and hypertension (210/90) secondary to polycystic kidneys The adrenals thyroid parathyroids and pancreas were grossly normal and the thymus

was atrophic The pituitary and pineal bodies and the brain were macroscopically normal In the testes there was no evidence of maturation of spermatozoa and the interstitial cells were decreased in number Microscopically the adrenal parathyroids and pancreas gland were apparently normal The thyroid contained many dilated acini filled with colloid and lined with cuboidal epithelium and was considered to be a typical colloid goitre The pituitary was histologically remarkable The anterior lobe was composed chiefly of basophilic and eosinophilic cells The marked predominance of the basophilic cells coloured the sections blue to the naked eye In serial sections no adenomata were seen Differential counts showed 42 per cent basophilic 36 per cent eosinophilic and 22 per cent chromophobe cells as compared with the normal 11 37 and 52 per cent respectively There was no evidence of any hyaline change in the basophil cells In the pars intermedia no colloid was seen however there was moderate invasion of the posterior lobe by basophilic cells No definite changes were found in the hypothalamus or brain microscopically except for diminution of Perkinje cells and loss of nerve cells in the granular layer of the cerebellum Anderson (1941) believes the significance of a preponderance of basophil cells in his and Griffith s cases may be significant In both however there was chronic kidney disease and in one severe hypertension which Cushing has associated with basophilia I doubt whether the autopsies on patients with the Laurence Moon Biedl syndrome have as yet elucidated the aetiology of this condition or the allied one of adiposo genital dystrophy The former condition is probably not a primary endocrine disorder

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Clinical Picture

A characteristic case suffers from mental defectiveness polydactyly pigmentary degeneration of the retina (retinitis pigmentosa) adiposity and hypogenitalism Adiposity is nearly always constant but of two brothers with the disorder one was

fat and the other thin and one adult became very thin after a fat childhood Adiposity is often of moderate amount but may be extreme Hypogonadism is usual but not constant Mental retardation is present in the great majority of cases ranging from mental deficiency to idiocy Polydactyly is nearly always present but may be absent in otherwise typical cases Retinal degeneration (retinitis pigmentosa) is reported by all observers Generally visual defect is noted in early childhood but in quite a number of cases it does not become apparent till later Optic atrophy is occasionally found Dwarfism is usual but normal height may be found Other rare complications are congenital heart disease microcephaly head nodding choreiform movements and muscular weakness One member of the family may have the complete syndrome and another perhaps one or two stigmata of it Symptoms are usually present from birth

Diagnosis

This is easy as defined above

Prognosis

This is poor and intercurrent infection not infrequent

Treatment

No fundamental treatment is possible

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CHAPTER VIII

ADIPOSE GYNANDRISM

Definition

A SYNDROME commencing in childhood and characterized by adiposity, delayed development of the penis and testicles a gynaecoid pelvis and feminine physical and behaviour characteristics

By definition the condition is limited to male children Its clinical counterpart in the female sex might be the type of adrenogenital syndrome that is manifest from puberty

The justification for my giving this disorder a name is the frequency of its occurrence and the failure to differentiate it from Fröhlich s syndrome or from uncomplicated adiposity The term gynandrism indicates a mixture of female and male characteristics

Pathology and Aetiology

Since the disorder is one of slow evolution autopsy material is lacking and the pathology remains conjectural The fact that genital development may be accelerated by injected gonadotrophic hormone suggests a pituitary or hypothalamic pituitary origin The clinical similarity with the syndrome of feminization starting in adult life raises the possibility of adrenal involvement but adrenal tumours in boys are associated with sexual precocity The frequency and familial incidence of this disorder suggests that genetic factors determine the endocrinopathy

Clinical Picture

Usually several members of a family if one includes two or more generations are affected The patients are fat pleasant children and more often than not have been fat from birth Sometimes at the age of puberty and sometimes years before the parents have noticed that the testes and penis are infantile and are not developing This is especially obvious at puberty in contrast to normal male children after making full allowance

for the hiding of the penis in the suprapubic fat Further the pubic and axillary hair may not appear until the late teens and even then the pubic hair is limited horizontally as in the

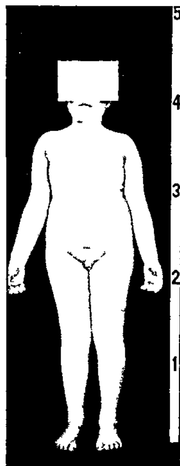


Fig 22 (a)

Fig 22 (a) This photograph shows the patient at the age of 8 and appeared in the first edition of this book under the heading of Childhood Adiposity which might develop into Frohlich's syndrome as the genitals appear small See fig 22(b) age 15

female and does not ascend on to the abdomen in triangular fashion The facial skin remains smooth and of fine texture and facial hair does not appear until late adolescence and even then is often of fine texture In adult life shaving may not be

necessary every day There is usually an absence of hair on the trunk

A fundamental clinical fact is that without any treatment

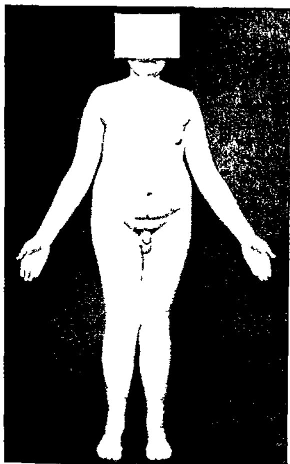


Fig 2 (b)

(b) This photograph shows the patient of fig 2 (a) at the age of 15 His penis and testes are now of normal size but the pubic hair is limited horizontally and the hair on the face is very scanty The breasts wide pelvis general behaviour gesture posture and emotionalism have feminine characteristics and the development illustrates a condition which the author has termed Adipose Gynandrism (See text)

these patients do develop some years later than puberty full sexual maturity and are capable of reproducing themselves

Their maturity however is not identical with accepted normality as is indicated above in the character of the secondary sexual hair Further the penis is ultimately often subnormal in dimensions But perhaps more important than this, they retain from childhood certain feminine or gynaecoid structural and behaviour characteristics Thus the pelvis is broad and open in fact gynaecoid The breadth of the pelvis is greater than that of the shoulders as in the female The glandular breast tissue may be well developed apart from the fatty deposition The latter is present on the face chest abdomen and thighs Lineae distensae are present on the lower abdomen and sometimes on the chest and axillae The gait because of the broad pelvis tends to be waddling as in certain types of females For this reason as well as the adiposity the patients are not good at games particularly those involving running They are however good swimmers and often excel Their stance is feminine and not infrequently they rest one hand on the hip Their facial expression is soft and sympathetic and a warm smile is frequent The voice is pleasant and often high pitched They are temperamental and not infrequently show musical or artistic talent Intellect is good and may be exceptionally high They are nearly always good company and popular but may have periods of depression Their height varies as does the rest of the population and they are neither especially short or tall There are many incomplete forms gradually merging into accepted normality

Diagnosis

The following already recognized syndromes have to be differentiated from the above condition of adipose gynandrism

(1) *Frohlich s syndrome* In childhood differentiation is not possible but in adolescence sexual maturation does not spontaneously occur in Frohlich s syndrome as it does in adipose gynandrism

(2) *Eunuchoidism* Here, too sexual maturation does not occur in adolescence. Further eunuchoids do not respond to a gonadotrophic stimulus as the primary defect is testicular

(3) *Cushing s syndrome* The differentiation here is more difficult since sexual maturation may be delayed in Cushing s syndrome The latter diagnosis is justified if there are other

features such as plethora polycythaemia purple lineae distensae hypertension osteoporosis and diabetes mellitus But when only one or two minor stigmata are present e g purple rather than white lineae distensae the less committal diagnosis of adipose gynandrism might well be applicable

(4) *Uncomplicated adiposity* Several clinicians have pointed out the rarity of Fröhlich s syndrome and the fact that the suprapubic fat in adipose children hides the penis They however push their contention still further without justification and claim that boys are really normal even though their sexual maturation has been delayed I have indicated above that this is frequently not the case and to emphasize this have given a label to the syndrome namely adipose gynandrism Nevertheless adiposity in childhood uncomplicated by primary or secondary sexual abnormalities or by gynaecoid skeletal build does occur and must be differentiated although its incidence in the absence of any other endocrine stigmata is probably rarer than is generally supposed

Treatment

Sexual maturity may be accelerated by gonadotrophic hormone Adiposity is treated along general lines (see appropriate section)

CHAPTER IX

SIMMONDS'S DISEASE

(Pituitary Cachexia Anterior Pituitary Deficiency)

Definition

SIMMONDS'S disease is a condition of anterior pituitary deficiency and secondary involution and hypofunction of the thyroid adrenal and sex glands manifested in typical examples by asthenia apathy cachexia amenorrhoea or impotence hypersensitivity to cold and to insulin a low basal metabolism and a very low level of 17 ketosteroids in the urine Morris Simmonds a Hamburg pathologist constructed a clinical picture in retrospect after observing at autopsy examples of ischaemic necrosis of large areas of the anterior pituitary gland in patients who died after parturition However the subsequent clinical features and obstetric background of severe parturition haemorrhage were illuminatingly discussed by Simpson as long ago as 1883

Pathology and Aetiology

The essential lesion is destruction of the anterior lobe of the pituitary gland and the commonest cause is thrombosis of the pituitary vessels following parturition associated with severe haemorrhage and not infrequently retained placenta Infection may be present but is not regarded by Sheehan (1937–9) as a fundamental factor in producing the thrombosis

Simmonds (1914) pointed out that the arteries to the anterior pituitary are end arteries and that emboli would therefore lead to infection and necrosis Reye (1926) thought the vascular process was thrombosis which he contended was especially liable to happen in an organ like the pituitary which underwent involution at parturition after being hypertrophied during pregnancy The penetrating and painstaking researches of H L Sheehan Director of Research at the Glasgow Royal Maternity Hospital have resulted in a valuable pathological and clinical elucidation He pointed out that the illustrations of Simmonds show what appear to be thrombi *in situ* in the capillary sinuses and suggests that it seems probable that in

these reports the word 'embolus' is used in the sense of a few organisms being carried in the circulation to the pituitary and there forming the nucleus of thrombus formation No satisfactory description has been given to suggest that the actual thrombus found obstructing the anterior pituitary vessel had been carried there by the arterial stream In fact in the absence of infective endocarditis or a patent foramen ovale it is difficult to see how an embolus could be carried to the pituitary blood vessels

In the majority of cases Sheehan states that the thrombi are not infective and predisposing factors are a peculiar distribution of the blood supply to the anterior lobe during pregnancy the rapid involution of the anterior lobe after delivery the increased coagulability of the blood during the puerperium and especially a sudden large haemorrhage during delivery Puerperal sepsis may be a complication The thrombosed sinuses as found by Sheehan were small and it was not possible to say whether they were functionally arterial or venous In the absence of any other cause for the necrosis it would appear that the thrombosis is the primary lesion In all cases even in those dying some time afterwards the necroses all appear to date from the time of delivery Characteristic necrotic findings are rarely discernable however if death takes place earlier than 14 hours after parturition The necrosis may be small large or almost complete but it usually spares the pars tuberalis the part just in front of the attachment of the stalk the region of the pars intermedia and a thin layer or small scattered islets just beneath the capsule Sheehan writes adopting arbitrary figures there will probably be no symptoms with a loss of less than 50 per cent of the gland the symptoms will be slight with a 60 per cent loss moderate with a 75 per cent loss and severe with a 95 per cent loss Judging from the histology of the pituitary in patients who died several years later from other causes it seems remarkable how small a portion of gland need remain undestroyed in order to carry on normal adequate function but this is quite comparable with our knowledge of other endocrine glands e g thyroid and pancreas

Other causes of destruction of the anterior lobe are craniopharyngioma (Farber 1940) chromophobe adenoma haemorrhage into a chromophobe adenoma (Aitken and Russell 1934)



(a)



(b)

FIG 93 CHROMOPHOBE ADENOMA X ray p ctures of pituitary fossa of two pat ents (a) Male aged 1 , (b) Male age 1 61 resulting in both cases in optic atrophy weakness and d sappearance of libido In both ca es operation arre te l the process but produce l or did not fail to prevent incomplete Simmon is s cachexia Te to terone re tore l appet te trength mu cu lar le elop ment an l libi lo with potency (Ref *Proc Roy Soc M* t (1947) xl 1 1 Di kson Wr ght A and Simp on S L Taylor J an l Simp on S L)

hypophysectomy for neoplasm cysts syphilis tuberculosis and unidentified granulomas (Glass and Davis 1944) and trauma e g bullet wound and fractured skull Lerman and Means (1945) record a case of epilepsy and Simmonds's disease following head injury, in which autopsy showed fibrosis of the anterior pituitary gland and quote another important case of Schereschewsky of Simmonds's disease following fracture of base of skull in which ultimate autopsy showed marked diminution in size of the anterior pituitary and of its cellular elements as well as haemorrhages in the floor of the third ventricle These findings give some basis to the hypothesis of a hypothalamic pituitary disturbance in cases of incomplete Simmonds's disease that appear to follow shock (Thompson 1938 Greene and Paterson 1943) The influence of the hypothalamus and higher cerebral centres on the anterior pituitary is also suggested by the cure of an apparent case of incomplete Simmonds's disease by leucotomy (Hemphill 1944) Whether or not this applies to the late stages of anorexia nervosa which condition so closely resembles Simmonds's cachexia will be discussed later (see Anorexia nervosa) but the initial cessation of menstruation following shock or acute anxiety must be due to a cerebral inhibition of the pituitary gonadotrophic stimulus

Inanition may in itself cause a failure of anterior pituitary function (see Gonad section and Drill and Burrill 1944) or produce symptoms which simulate the condition Leyton (1946) in an important study of the effect of deficient diets in a prisoner of war camp noticed features common to anorexia nervosa and Simmonds's disease e g bradycardia 47 low blood pressure 90/55 mm Hg subnormal temperature 35 7 C and a susceptibility to pulmonary tuberculosis but the blood sugar was normal or only slightly lowered

Other Endocrine Glands

Thyroid Partial or complete atrophy of the thyroid is found and its weight is less than half of the normal 25 gm (Sheehan 1939) The alveoli are scanty and atrophic with little or no colloid therein and there is gross fibrosis round celled infiltration and numerous lymphoid follicles

Suprarenals The cortex is atrophied and the zona glomerulosa and reticularis are very thin and sometimes absent There

is rarely any fibrosis although the capsule may be thickened Lipoid is usually present in the cortex and sometimes in normal amounts but there may be none The medulla is normal

Gonads The ovaries and uterus may be completely atrophic and fibrotic or incomplete maturation of Graafian follicles may be found The testes may be minute and atrophic (Rowlands and Simpson 1942) with complete disorganization of the normal structure and no evidence of the presence of spermatozoa or spermatogonia

Parathyroids Sheehan (1939) found the parathyroids rather small or very fatty or fibrous

Pancreas The islets of Langerhans might be very small or apparently normal

Viscera

Splanchnomicria in contrast to the splanchnomegaly of acromegaly is characteristic the stomach intestines lungs heart liver and spleen &c being smaller than average without necessarily showing any pathological changes The heart may show brown atrophy There is a striking absence of fat

Incidence

In view of the importance of parturition haemorrhage as an aetiological factor the disease is much more frequent in women than in men It has always been regarded as a very rare disease but if one includes incomplete forms following pregnancy it is by no means as rare as was formerly believed

Clinical Picture

The condition is usually one of adult life but rarely—when for example it is due to a slow growing craniopharyngioma as in a case under the observation of the writer—the initial symptoms are seen in childhood as a failure of normal somatic and sexual development (Rowlands and Simpson 1942) but even so the characteristic picture of Simmonds's disease is not fully developed until adult life

In the majority of patients the disease starts from a parturition which is associated with severe haemorrhage and collapse frequently with a retained placenta and sometimes with puerperal sepsis These serious concomitants overshadow any

specific manifestations of a sudden destruction of pituitary function but it is soon observed that the recovery of the patient does not take a normal course

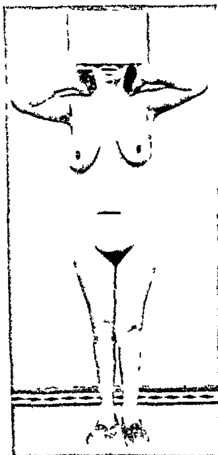


FIG 24 SIMMONDS'S CACHEXIA (I f re ll y D D [illegible] Ley) Woman of 30 whose pregnancy 3 years previously was followed by amenorrhoea l[illegible] f pubic hair loss of weight and weakness bradycardia blood pressure 90/70 typical insulin sensitivity curve responded well to testosterone

More specifically there is a complete absence of mammary activity and of lactation in many patients and Lévy–Solal (1932) has described hypoglycaemic shock after delivery when

the blood sugar may be as low as 50 mg per 100 c cm (Sheehan) However in the majority of patients there may be no diagnostic specific features and the condition may or may not be suspect until the more chronic picture evolves



FIG 25 SIMMONDS'S CACHEXIA (This patient was referred to me by Dr C A Birch) Woman of 57 who following the birth of twins at the age of 32 lost pubic and axillary hair and never menstruated again She had several attacks of hypoglycaemic coma and finally died in one of these Autopsy showed complete atrophy of the anterior pituitary lobe and secondary involution of the adrenal cortex

General symptoms and signs Behaviour is often characterized by apathy and inertia and sometimes by phases of irritability or somnolence associated with hypoglycaemia The patient appears indifferent to her surroundings and normal social activities She lacks initiative and spontaneity and may become careless in her dress sluggish in thought and slow in speech Questions may not be answered until after a long latent period She sometimes appears stupid or absent minded and may stare into space for long periods or lie in bed Sheehan states that more marked mental symptoms are rather frequent in the last few months ranging from oddness or alternating attacks of excitement or depression up to definite insanity In moderate cases the patient complains of excessive weariness on slight exertion Muscular atrophy and atony are concomitant features Sensitivity to cold may be very marked even when warmly dressed The patient tends to get completely under the bedclothes The face takes on a pallid appearance even with absence of anaemia

—a pallor which may be regarded as in striking contrast to the plethora of Cushing's syndrome. The skin may be delicate and fine in texture with an involution of sweat and sebaceous glands but some patients develop a wrinkled skin and an appearance resembling the progeria of Hastings Gilford (see below). In others there is a tendency to mucoid infiltration of the skin as in myxoedema. The hair of the head loses its lustre and becomes dry, thin and brittle. Its colour may also change, e.g. from a dark brown to a light brown. The eyebrows become thin especially in the outer half. The pubic and axillary hair is usually completely lost. It may be partially retained but thinned.

In classical cases there is a striking loss of subcutaneous fat and feminine contours accentuated by atrophy of the mammary glandular tissue. This loss of fat and weight is nearly always associated with anorexia or decrease in appetite. However wasting is not an invariable feature of incomplete Simmonds's disease. Associated with a diminished appetite is a lessening of thirst and water intake and output. Achlorhydria is present in some 50 per cent of patients. Constipation is common. Decay and loss of teeth is a feature of the worst cases and may be quite rapid in onset and completion.

Gonadal function. In the female amenorrhoea is the commonest manifestation of gonadal failure and menstruation may never return after parturition. In other patients menstruation is scanty and at long irregular intervals. Very rarely it may be normal and another spontaneous pregnancy occur. In the male libido and potency disappear, the testes become atrophic.

Cardiovascular. Bradycardia is almost invariable and the blood pressure is characteristically low but occasionally normal. The electrocardiogram shows a low voltage.

Pulmonary. There are no abnormal pulmonary changes in uncomplicated cases but tuberculosis sometimes supervenes. It may then be insidious and silent and is often unsuspected, especially as the pulse rate tends to remain slow and the temperature sub-normal. Broncho-pneumonia may also supervene in the later stages and prove fatal.

Skeletal. Children when affected with a craniopharyngioma fail to grow and a type of dwarfism results. X-rays show a delay or complete absence of union of the epiphyses of the long

bones In contradistinction to acromegaly the hands and feet are diminutive and the fingers delicate and tapering Bony absorption and retraction of the lower jaw may occur in adults so that the opposite condition to prognathism results the teeth *decaying and falling out*

Metabolism The basal metabolism is almost invariably low Sheehan states that it lies between minus 25 and minus 33 per cent in the first 15 years after onset and later may be minus 40 per cent In my experience the degree of depression of metabolism *does not depend upon such duration Further it is* important to realize that in some patients showing a definite but incomplete syndrome after parturition the basal metabolism may be only slightly lowered e g minus 12 per cent The temperature is usually subnormal and may be very low 96° C *Blood cholesterol* values *are sometimes raised but not in my* experience as raised to the same extent as in myxoedema even when the basal metabolism is comparably lowered

Carbohydrate metabolism Carbohydrate tolerance curves are not constant in Simmonds's disease The fasting blood sugar is usually low and the most characteristic curve is a flat one showing a prolonged plateau at values only slightly above normal and not returning to subnormal values until after 2 hours

In a patient with complete surgical hypophysectomy for a pituitary tumour Hart and Mageday (1941) found the following carbohydrate tolerance curves on two occasions samples being taken at intervals of *half an hour* (and sometimes *1 hour*)

First test
B S 34 mg (fasting) 65 mg 98 mg missed 118 mg missed 34 mg (3 hrs)

Second test
B S 66 mg (fasting) 111 mg 125 mg 111 mg 108 mg

Third test
B S 46 mg (fasting) 70 mg 76 mg discontinued after the one hour

Patients with Simmonds's disease give similar carbohydrate tolerance tests although there is a good deal of variation according to the degree and extent of anterior pituitary deficiency e g

56 mg (fasting) 85 mg 105 mg 120 mg 98 mg 70 mg

The hypoglycaemic values and the failure of the blood sugar to rise to normal post prandial value is ascribable to the absence of the pituitary diabetogenic hormone and the adrenal cortex diabetogenic hormone. These deficiencies also explain the results of insulin sensitivity tests (see below). The persistent plateau type of carbohydrate tolerance curve may be due to slow intestinal absorption.

Sometimes with Simmonds's cachexia normal or impaired carbohydrate tolerance curves are obtained, the latter presumably due to involution of pancreatic islet tissue, as is sometimes found at autopsy, and which is ascribable to the destruction of the pituitary pancreatrophic hormone. Another possible explanation of such atypical tolerance curves is the fact that the low food intake (including carbohydrates) might produce endogenous insulin resistance, but the insulin sensitivity curves still remain characteristic of Simmonds's disease.

Insulin sensitivity tests give a typical response in most cases, namely, a normal rate of fall of blood sugar after intravenous insulin, but a very tardy recovery of pre-insulin blood sugar values, this tardiness being referred to as hypoglycaemic unresponsiveness (Fraser and Smith, 1942).

The patient should be well fed (as far as is possible) for 3 days before the test. Then, after taking a fasting blood sugar specimen, insulin is injected intravenously. For normal people 0.1 units of insulin per kilogram body weight is the dosage, but for suspected Simmonds's disease a characteristic curve will be given with half this dosage (or even a third). The reduction of the standard insulin dosage is advisable to avoid too severe a hypoglycaemic response endangering life. It may be necessary to interrupt the test to give glucose or inject adrenaline. Capillary blood is taken at intervals of 20, 30, 45, 60, 90 and 120 minutes after the insulin injection. Typical values are (mg per 100 c.c.):

Normal control	100 (fasting)	45	52	60	82	95	105
Simmonds's	70 (fasting)	36	38	42	52	54	58

The initial fall of blood sugar is normal, allowing for the lower fasting basis, by calculating as a percentage of the initial blood sugar value, but there is a marked delay in returning to the initial blood sugar values, and in severe cases, especially if the standard test dose of insulin is not drastically reduced, the

patient s own resources may be quite unable to maintain let alone increase the low blood sugar concentration reached after the first 30 minutes and a hypoglycaemic crisis may develop Apart from the absence or severe diminution of the pituitary and adrenal cortex diabetogenic hormones it must be remembered that the liver of a hypophysectomized animal is often depleted of glycogen Since however these patients usually respond to adrenaline hepatic glycogen stores are apparently present and mobilizable by an exogenous stimulus

With anorexia nervosa the insulin sensitivity test may be normal but in severe cases it may be identical with that of Simmonds s disease

In myxoedema there may be some retardation of the subsequent rise of blood sugar (relative hypoglycaemic responsiveness) but there is also a delayed initial fall of blood sugar concentration (i e insulin resistance)

The above observations on the disturbance of carbohydrate metabolism in Simmonds s disease are of great clinical importance since spontaneous attacks of hypoglycaemic crisis may occur at any time and may prove fatal Some peculiarities of behaviour and attacks of somnolence are also ascribable to hypoglycaemia and in the course of conducting insulin sensitivity tests I have observed their reproduction In one case the patient had amnesia for the whole period of the test although she had answered questions during it and had not lost consciousness

17 ketosteroid assays The assay of urinary 17 ketosteroids measures in blunderbuss fashion a variety of androgens derived from gonads and adrenal cortex Normal values vary to some extent with the technique employed but may be taken as being 5 to 15 mg per day

In Simmonds s disease Fraser and Smith (1942) found extremely low values under 0 5 mg per day but in mild cases values are below 2 mg In their four cases of anorexia nervosa assays ranged between 2 7 and 14 7 mg per 24 hours I have had one patient with anorexia nervosa excreting 1 9 mg and another 2 4 mg per day I have also had patients with incomplete Simmonds s disease excreting more than 2 mg per day There is no doubt however that values of less than 2 mg per day in a case of suspected Simmonds s disease are a supporting

factor and values of less than 0 5 mg a strong one Low values may be found in Addison s disease (which see) In primary myxoedema Fraser and Smith (1942) found values very low varying between zero and 1 7 mg per 24 hours These very low values are difficult to explain theoretically as the thyroid is not a source of 17 ketosteroids and the adrenal cortex is not atrophied in primary myxoedema

Adrenal cortex insufficiency Such insufficiency would be anticipated in Simmonds s disease because of the atrophy or involution of the adrenal cortex found at autopsy The low 17 ketosteroids in the urine is one expression of such an adrenal cortex failure but as with the protean symptomatology of Simmonds s disease it is not possible to say more than that the adrenal cortex insufficiency contributes to producing the clinical features e g hypotension hypoglycaemia weakness &c It is perhaps remarkable that pigmentation is usually not present in Simmonds s disease and is certainly never found on the mucous membranes Occasionally there is some patchy brown pigmentation on the chest or neck but it rarely if ever has the characteristic intensity and distribution of that found in Addison s disease

The serum values for sodium potassium and chloride rarely approximate to those found in Addison s disease but the Kepler test of adrenal function dependent upon water and chloride excretion not infrequently gives values as low as those found in Addison s disease I have found this to be the case in six patients and McCullagh and colleagues (1943) record figures between 1 4 to 12 8 (normal index over 25) Stephens (1940) also found increased chloride excretion

In the course of investigations over the past six years on Addison s disease and Simmonds s disease I found (unpublished) that the Kepler test result usually but not invariably corresponded with poor renal function tests (in the absence of renal disease) Beaumont and Robertson (1943) have described poor renal function in Simmonds s disease their papers being entitled Pituitary Hypothyroidism with Impaired Renal Function

Diagnosis

Amenorrhoea weakness apathy poor appetite loss of weight bradycardia hypotension low basal metabolism and

temperature and hypersensitivity to cold are present in a characteristic case and frequently these symptoms follow a parturition associated with severe haemorrhage It is now accepted that anorexia and loss of weight are not invariable and the maintenance of weight should not exclude the diagnosis if other features are present I am unable to confirm that some patients may even gain weight but such is claimed

It is important to remember that the majority of cases are examples of an incomplete syndrome and may well be missed unless the condition is kept in mind as a sequel of complicated parturition Amenorrhoea for example was formerly considered to be an invariable feature but this is not so and undoubted cases have even become pregnant spontaneously However the presence of normal menstruation makes the diagnosis much less certain I attach considerable importance to bradycardia but it is claimed by other observers that it is not invariable The same applies to low blood pressure and the basal metabolism is not necessarily severely lowered

Simmonds s disease may be due to neoplasms or granuloma of the pituitary gland and it will be remembered therefore, that parturition is not the only cause and that the disorder may also occur in men If the condition starts in childhood e g a slow growing destructive craniopharyngioma infantilism will be the background on which the adult syndrome will be superimposed

The disease is often insidious in onset even when due to a post parturition thrombosis but it may be acute and fatal e g haemorrhage into a chromophobe adenoma On the other hand, it may be present and pass unrecognized for 30 or more years

A number of conditions will be separately considered in the following differential diagnosis and in some it will be indicated that there we are dealing with a question of nomenclature rather than differential diagnosis

Differential diagnosis This includes

(1) *Addison s disease* From the fact that both in Addison s and Simmonds s disease the adrenal cortex is functioning poorly much of the symptomatology is common to both diseases Pigmentation is usual in Addison s disease and is widespread sometimes including the mucous membranes but in

acute cases or in fair people pigmentation may be minimal In Simmonds's disease pigmentation is usually absent but there may be patches on the chest and neck and freckles Bradycardia is rare in Addison's disease and the basal metabolism is not appreciably lowered except in crisis Pubic and axillary hair is not lost in Addison's disease and menstruation is not infrequently normal

(2) *Myxoedema* This diagnosis is often erroneously made Thyroid insufficiency is one feature of the disease but not the whole clinical picture (see above) The 17 ketosteroids are below 2 0 mg per day in both conditions The blood sugar is usually not low in myxoedema there is a slower fall in blood sugar after intravenous insulin but a normal or slightly delayed subsequent rate of recovery of blood sugar values Pubic and axillary hair is not lost Examples of Simmonds's disease have been described under the title of pituitary myxoedema —a confusing term which should not be used

Myxoedema will respond dramatically to thyroid whereas in Simmonds's disease the response is only partial and sometimes the patient is made worse A more experimental approach will show that the basal metabolism &c will respond to thyrotrophic hormone in Simmonds's disease whereas in myxoedema it is completely uninfluenced the thyroid being unable to respond

(3) *Snapper's syndrome* Snapper Groen Hunter and Witts (1936) described a syndrome characterized by hypogonadism alopecia depression of metabolism and anaemia apparently due to a lesion of the anterior lobe of the hypophysis Four patients were males and two females their ages varying from 42 to 58 years One had a chromophobe adenoma of the pituitary and in the others a pituitary lesion was postulated from the symptomatology In two men the syndrome had commenced in childhood The anaemia might be hypochromic responding to iron or hyperchromic responding to liver In three patients there were symptoms of sub acute combined degeneration of the cord Witts (1942) later described two further cases under the heading pernicious anaemia and pituitary insufficiency

In Simmonds's disease the blood picture may be normal but hypochromic and hyperchromic anaemias are met with Apart from the results of achlorhydria the significance of thyroid deficiency in haemopoiesis must be borne in mind (see Thyroid

section) Some 50 per cent of patients with Simmonds's disease have achlorhydria

Snapper's syndrome may be regarded as a variety of Simmonds's disease rather than a separate entity I have called the syndrome after Snapper because the title is much easier to use than the rather verbose 'achlorhydria anorexia and sub acute combined degeneration in pituitary and gonadal insufficiency', and because Professor Snapper has made many valuable contributions to endocrinology

(4) *Anorexia nervosa* This condition is a neurosis and not an endocrine disorder Autopsy findings are quite different from those in Simmonds's disease Apart from the involution (or atrophy) of the ovaries and uterus the endocrine glands are usually normal (Brosin and Apfelbach 1941 Conybeare 1930) but in one autopsy the acidophil cells were small and poorly granulated (Richardson 1939) Apart from morbid histology there is evidence of apparent impaired function of the pituitary, thyroid and adrenal cortex as in Simmonds's disease and this led to the postulation of a functional Simmonds's disease (Sheldon 1937) a term which is probably best avoided Reiss (1943) found an absence of gonadotrophic and corticotrophic hormone in the urine of a patient with anorexia nervosa but a reappearance of these hormones after the patient's recovery In this patient also the urinary 17 ketosteroids rose from 6 8 mg to 12 0 mg per day after recovery The 17 ketosteroids may be much lower in anorexia nervosa e g 2 5 mg although I have never found a value below 1 5 mg whereas in Simmonds's disease values below 1 5 mg are usual if the syndrome is completely developed In incomplete Simmonds's disease the 17 ketosteroids may be above 2 mg per day and this differentiation from anorexia nervosa is by no means absolute The Kepler test of adrenal function in anorexia nervosa is usually negative

The carbohydrate tolerance curve and insulin sensitivity curves of anorexia nervosa may be identical with those obtained with Simmonds's disease but on recovery with psychological treatment such tests when repeated give normal figures It seems probable therefore that the disturbance of carbohydrate metabolism in anorexia nervosa depends on chronic inanition rather than on endocrine disturbance Experi

mentally it has been shown (see Physiology section Adrenals and Sex Glands) that avitaminosis produces changes in the endocrine glands. The amenorrhoea of anorexia nervosa gives way to normal menstruation after psychological cure resulting in better nourishment, but a more rapid hypothalamic pituitary inhibition is the most likely cause of the initial amenorrhoea as this may be the first symptom. Later inanition and hypovitaminosis may play a part. Although there is still much work to be done in the investigation of endocrine gland function in anorexia nervosa and on their morbid anatomy, there seems to be sufficient evidence to conclude that some of the symptomatology of anorexia nervosa is secondary to a hypothalamic pituitary disturbance which is caused by a primary psychogenic disturbance and complicated by the further effects of inanition. The latter can however by itself cause amenorrhoea, impotence, bradycardia, hypotension, low basal metabolism and some lowering of the blood sugar (*Leyton 1946*).

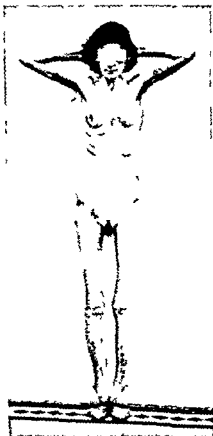


Fig. 6. Anorexia Nervosa. Girl of [illegible]4 years; amenorrhoea and loss of weight; sensitive, fretful and emotional disturbance preceded onset. Illustrates that in the late stages pubic and axillary hair can become very scanty, as in Simmonds's cachexia. 17-ketosteroids can also become quite low in concentration, namely [illegible] mg. in 24 hours. Unlike Simmonds's cachexia the patient was restless and active in spite of her emaciated condition.

Although the late stages of anorexia nervosa and Simmonds's disease are almost identical in their major manifestations, there should rarely be any difficulty in making a differential

diagnosis and this is best done on clinical reasoning and observations. Anorexia nervosa usually occurs in adolescent unmarried girls, whereas Simmonds's disease frequently follows parturition with haemorrhage. In anorexia nervosa there is often a history of psychic trauma or severe mental disturbance and almost invariably other manifestations of a neurosis; the patients are restless and often voluble; they are also optimistic, enterprising and active (except in the latest stage), their activity being entirely out of proportion to their weak, wasted physical state. In Simmonds's disease the patients are usually apathetic and listless. Although amenorrhoea is common to both conditions, it is only in Simmonds's disease that the pubic and axillary hair is completely lost (except in incomplete cases); in anorexia nervosa the sexual hair is often present and may be considerably reduced but it is rarely completely lost. In anorexia nervosa there may be general growth of down or soft hair over the body or face, but such does not occur in Simmonds's disease.

Anorexia nervosa often responds to psychotherapy and environmental changes and some patients may swing so far in the opposite direction as to become grossly adipose. Psychotherapy is completely ineffective in Simmonds's disease, which however responds to hormone substitution therapy. The latter is relatively ineffective and disappointing in anorexia nervosa, except perhaps oestrogens in their limited sphere.

Depressive anorexia associated with the psychoses may occur at any age and give a physical picture resembling anorexia nervosa. *The condition is also wrongly diagnosed as* Simmonds's disease.

(5) *Progeria.* In 1904 Hastings Gilford introduced the term *progeria* (prematurely old) to differentiate a form of infantilism associated paradoxically with senile characteristics. If this conception is accepted in its broad outline, progeria is not so very rare and may be a concomitant of Simmonds's disease which has commenced before puberty (see Rowland's and Simpson's case, Figs. 27 and 28). However, Hastings Gilford's case (male, age 18) was almost identical with one (male, age 34) described by Jonathan Hutchinson in 1886 and again by *Hastings Gilford in 1904. Both had very specific features, e.g.* complete baldness of head, absence of mammae and absent

eyelashes Gilford's case had normal sexual development and at autopsy there were no changes in the pituitary adrenal or thyroid glands In 1914 Gilford could only find one further

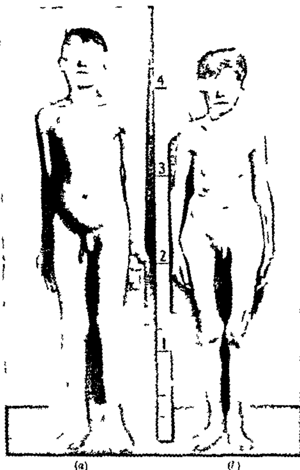


FIG 27 SIMMONDS'S CACHEXIA (a) Control aged 10 (b) The patient aged 43 emaciation infantile genitalia no secondary sexual characteristics infantilism subnormal temperature basal metabolic rate minus 40 bradycardia hypotension hypoglycaemia ununited epiphyses A craniopharyngioma destroying the whole of the anterior pituitary gland (Case of Drs R A Rowlands and S L Simpson)

case (published in 1910 by Variot and Pironneau) in medical literature It seems therefore that progeria as described by Hastings Gilford must be regarded as a museum rarity and

since there is much confusion in the literature on this subject I append essential extracts of Hutchinson's and Gilford's papers and photographs of their cases Progeria meaning an appear

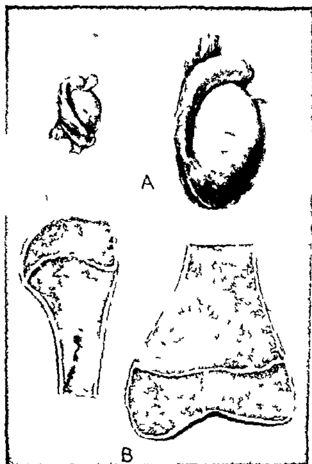


Fig 28 Simmonds's Cachexia (a) Testis and epididymis of patient in Fig 27 compared with that of a normal adult of same age on right (b) Section through long bones to illustrate failure of epiphyses to unite

ance of senility complicating infantilism is not uncommon in organic anterior pituitary deficiency commencing before puberty When anterior pituitary deficiency commences in adult life the patient may develop an appearance 20 years older than her age but progeria should not be applied here as there are no features of infantilism

Cases of Progeria Jonathan Hutchinson s case described in 1886 under the heading Congenital Absence of Hair and Mammary Glands with Atrophic Condition of the Skin and its Appendages A boy aged 3½ presented a very peculiar withered or old mannish appearance all his features being thin and pinched His fingers were shrivelled and dusky His head was large and the anterior fontanelle not quite closed the scalp was exceedingly thin and with the exception of a quantity of down was quite bald It looked semi transparent and tight and the veins coursing it were everywhere conspicuous His teeth were all out The integument everywhere was very thin and the subcutaneous fat absent except in the genital region The testes and penis were normal There were no mammary glands and no nipples and their sites were occupied by patches of scar The patient had five normal older sisters and no brothers His mother had had alopecia totalis since the age of 6 with a slight degree of recovery

Gilford recorded in 1904 that Hutchinson s patient was seen at the age of 15 years and bore a striking resemblance then to Gilford s own case He died at the age of 1, from intercurrent infection but there was no autopsy

Hastings Gilford s case described under the title of Progeria a Form of Senilism A R a fifth male child with four normal brothers and five normal sisters was said to have been a normal baby At 6 months he began to cut teeth the hair of his head began to fall out his nails to shrivel and his fat to diminish At 18 months his shoulders became rounded chest narrow and the cranium large in proportion to the face giving a hydrocephalic impression He was a lively good tempered child but easily fatigued He walked at age 2 but was backward in speaking Dentition was retarded He had chronic flatulent dyspepsia and was always dyspnoeic He was first seen by Gilford in 1891 when aged 14 and his appearance when he came into my room was suggestive either of a child of five or a wizened and dwarfish old man This appearance of senility was occasioned not only by his baldness and by the wrinkled condition of his skin but by the leanness of his figure and by the lack of vivacity Thin thighs and a stiffness of gait still further increased his resemblance to a decrepit old man But what contributed more than all this old mannish appearance was the withered and juiceless look of his skin the absence of colour in the scanty hair on his scalp and the piping tone of his voice A few scattered downy hairs were on the eyelids and eyebrows There was no vestige of mammary glands and the nipples were unusually small The skin of the body was thin dry and pliable but he often sweated profusely His intelligence was uncommonly good and his ideas were those of a man He had poor muscular development and was easily fatigued Although he had had no schooling he could read easy sentences The anterior fontanelle were open 5 mm The lips were thin and compressed The testicles were descended and of medium size (no mention is made of the size of the penis) When he had passed the age of 16 he had wet dreams and spermatozoa were detected He died in an attack of diarrhoea and sickness



Fig 29 (a)

Fig 29 Progeria (a) Jonathan Hutchinson's case boy aged 1½ years also seen by Hastings Gilford



Fig 29 (*b*)

(*b*) Hast ngs G lford s case boy aged 1 (See d cription page 87) (*Med Cl Trans* (1897) lxxx 17)

age 18 *P M* Scanty subcutaneous fat anterior fontanelle closed skull very thin 2 mm Pineal and pituitary bodies apparently normal a persistent and hypertrophied thymus thyroid normal microscopically atheroma and calcification in the walls of the aorta and blocked coronary vessels The suprarenal bodies were both of perfectly healthy appearance

Course and Prognosis

The course of Simmonds's disease in the absence of treatment is usually progressively downhill with a fatal outcome in months or years Sometimes deterioration is slow and even when the disease starts before puberty with a craniopharyngioma death may not occur before the age of 43 (Rowlands and Simpson 1942) Incomplete forms of the syndrome following parturition may remain alive and even reasonably well for 20 or 30 years Occasionally rapid deterioration leads to death in a few weeks Treatment in the less acute cases may produce considerable amelioration An appreciable degree of spontaneous recovery may occur

Treatment

Surgical conditions such as intracranial neoplasms require surgery but the majority of cases need hormone substitution therapy and the latter is also called for after surgical hypophysectomy

Since nearly all the endocrine glands are affected it is difficult to decide in any one case which form of therapy to use and it is technically and practically impossible to employ complete replacement therapy My own experience with several cases is as follows

(1) *Thyroid* Thyroid extract by mouth may help partially in some patients but in others may prove harmful and even precipitate a crisis It should therefore be used with caution commencing with small doses and is best deferred in the more severe cases until some general improvement is made by other means Thyrotrophic hormone is dangerous in these cases

(2) *Oestrogens* Oestrogens by mouth may not be well tolerated but by injection or subcutaneous implantation they prove helpful generally apart from the possibility of restoring the uterus to normal size and producing a bleeding They should be given in large doses e g 5 mg oestradiol benzoate

injected daily Restoration of fluid to the subcutaneous tissues appears to be a good effect

(3) *Progesterone* In large doses this hormone also appears to be generally beneficial but it is very expensive

(4) *Testosterone* I have found testosterone propionate by injection (e g 25 mg on alternate days) or implantation (400 mg) a very useful therapeutic measure and probably the best single therapy available This is true not only for men but for women Androgens are derived from the adrenal cortex as well as from the gonads and in Simmonds's disease they are very low as judged by urinary excretion This makes the therapy logical as substitution therapy Further androgens are anabolic producing nitrogen retention abolishing creatinuria and resulting clinically in increase of strength weight and well being Werner and West (1943) have obtained similar results with methyl testosterone given orally e g 5 mg t d s and this is also my experience

One disadvantage of androgen therapy is the possible production of acne some hairiness of the face and deepening of the voice but these untoward results are unlikely to result from moderate dosage Androgens also tend to maintain an inhibition of ovarian function and cannot therefore be regarded as the ultimate treatment although so beneficial in many cases

(5) *Adrenal cortex therapy* When a Kepler test shows severe adrenal inadequacy desoxycortone may be given with considerable benefit as in Addison's disease although the result is not as good as in the latter condition Corticosterone the diabetogenic hormone of the adrenal cortex counteracts the hypoglycaemia and insulin sensitivity of the hypophysectomized animal It is not yet available for clinical use but some cortical extracts are assayed for their influence on carbohydrate metabolism and therefore contain corticosterone like substances Since a crisis in Simmonds's disease is often hypoglycaemic in origin and the patient may die in hypoglycaemic coma intravenous glucose should be immediately administered and followed by 20 c cm of adrenal cortical extract injected intramuscularly daily or thrice daily until the more immediate recovery is attained

(6) *Pituitary hormones* Pituitary gland is ineffective by mouth By injection thyrotrophic hormone is effective as

judged by the effect on basal metabolism but it is dangerous and not clinically satisfying. Patients are often allergic to gonadotrophic hormones and I have not found them useful in Simmonds's disease. Hemphill and Reiss (1944) claimed benefit from pituitary corticotrophic hormone.

(7) *Insulin*. This is often prescribed to produce fattening but the patient is already hypoglycaemic and insulin hypersensitive and its use is contra-indicated. In practice hypoglycaemic attacks are precipitated.

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CHAPTER X

CUSHING'S SYNDROME

Definition

This syndrome consists of virilism (females) or feminism (males) associated with adiposity plethora hypertension diabetes mellitus and other features and apparently caused by a variety of pathological lesions namely adenoma or carcinoma of the adrenal cortex adenoma or carcinoma of the anterior pituitary basophil cells arrhenoblastoma of the ovary and carcinoma of the thymus all of which lesions are in most if not all cases accompanied by histological or biological evidence of hypercorticalism (adrenal cortex hyperfunction with or without obvious hyperplasia) and hyalinization of the pituitary basophil cells The functional significance of the latter histological findings is still undecided The above qualification must also be qualified by the statement that a basophil adenoma occasionally appears to arise from the pars intermedia and not the pars anterior of the pituitary gland

Cushing has described his eponymous syndrome as follows

The disorder is characterized by a rapidly acquired plethoric adiposity affecting the face neck and the trunk the extremities being spared It is associated in women with hypertrichosis and amenorrhoea Other characteristic features are vascular hypertension purplish striae distensae of the abdomen and acrocyanosis with cutis mammorata of the extremities It is often accompanied by hyperglycaemia and a peculiar softening of the bones of the skeleton has been commonly found at autopsy In its extreme forms the malady has often been encountered in young adults and the average duration of life in the fatal cases has been something over five years

History

There is no doubt whatsoever that the clinical picture of Cushing's syndrome has been known to physicians for some 50 years and has been frequently reported under a variety of clinical names in the literature particularly in France (Achard and Thiers 1921) It was however the keen clinical and pathological observation of Cushing as well as his intensive study of the literature which resulted in the crystallization and separation of a distinct clinical entity so ably and dramatically

presented in his classical monograph of 1932 In this monograph Cushing recorded in retrospect five cases in women from the literature and added two of his own and four cases in men to which he added one of his own The special significance of this monograph lies not so much in the excellent clinical descriptions of which there had been quite a number of special merit (e g Launois 1911 Turney 1913 Anderson 1915 and Parkes Weber, 1926) but in the title chosen for the presentation — The Basophil Adenomas of the Pituitary Body and their Clinical Manifestations This title was chosen not only to draw attention to the finding of a basophil adenoma in some of these cases which finding had been previously recorded by others e g Erdheim (1903) and Anderson (1915) but to a thesis put forward for the first time by Cushing to the effect that his syndrome was due to a pituitary basophil adenoma in the same way as acromegaly was due to an eosinophil adenoma We shall see in the pathological section that this thesis has received not unjustifiably critical examination As to the name of the syndrome which had previously been referred to as the fat bearded diabetic woman and other names indicating a poly glandular disease Bishop and Close (1932) of Guy s Hospital first suggested the title Cushing s syndrome in describing an excellent example of it

Pathology

An important definite and relatively frequent lesion is adenoma or carcinoma of the adrenal cortex or of an accessory adrenal gland or adrenal rest Since this occurs in the absence of hypertrophy or in the presence of atrophy of the remaining adrenal gland(s) it is unlikely that this neoplasm is always an expression of adrenal cortical hyperplasia secondary to a pituitary stimulus It is more probable that such a neoplasm is in some cases at least a primary lesion comparable to other primary neoplasms of endocrine glands If such be the case it might well be asked why should the resulting syndrome be so much richer in symptoms than the adrenogenital syndrome which latter is also due sometimes to an adrenal cortical neoplasm? Further it might be asked why in the case of Cushing s syndrome does one find so frequently if not always hyalinization of the basophil cells of the pituitary gland? The

answer surely must be as suggested by the writer in 1934, and in the first edition of this book that hyperfunction (neoplastic or otherwise) of the adrenal cortex influences the pituitary basophil cells either in the direction of basophilia with or without adenomatous formation or by vacuolization and hyalinization of the basophil cells It is known that adrenalectomy (or Addison's disease) produces a decrease in the number of basophil cells To evaluate the above suggestion one must consider (1) the function of the basophil cells and (2) the significance of hyalinization of basophil cells

(1) *Function of the basophil cells* There seems to be sound *experimental evidence that the basophil cells secrete the gonado* trophic hormones

(*a*) Castration in rabbits mice &c produces a striking increase in size and number of the basophil cells of the anterior pituitary gland and at the same time a considerable increase in the gonadotrophic power (including ovulation) of such a gland when implanted into immature rabbits or mice as compared with a normal gland (Smith Severinghaus and Leonard 1933)

(*b*) The above (*a*) is true of bilaterally ovariectomized women and less strikingly so of menopausal women (Biggart 1935)

(*c*) Adrenalectomy or destruction of the adrenal cortex by disease (Addison's disease) leads to *a decrease in the* number of basophil cells (Crooke and Russell 1935) and a decrease in the gonadotrophic power of the pituitary gland as judged by involution of the sexual organs (see section on adrenalectomy)

(*d*) The injection of gonadotrophic hormones of pregnancy *urine or serum* (Severinghaus 1934) *or* of oestrogens (Baker and Everett 1944) or of androgens (Wolfe and Hamilton 1939) leads to degranulization and vacuolization of the basophil cells

Although the above evidence appears conclusive enough it does not mean that the basophil cells are the only cells that secrete gonadotrophic hormone On the contrary there is some evidence that eosinophils may also do so under certain conditions Thus Haterius (1932) found that pregnancy in the rat was associated with the appearance of eosinophil pregnancy

cells which persisted as long as corpora lutea persisted and therefore appeared to secrete gonadotrophic luteinizing hormone The pregnancy cells in women are also eosinophilic (Biggart 1935) On the other hand acromegaly due to an eosinophil adenoma is associated with hypoganodism amenorrhoea and absence of libido

(2) *The significance of hyalinization of the basophil cells (Crooke)* Crooke (1935) was unable to confirm Cushing s hypothesis that a basophil adenoma or even a numerical increase in the number of basophil cells was present in all or even the majority of cases in which Cushing s clinical syndrome was found He noted however that whether the gross pathology consisted of an adrenal cortex tumour a basophil adenoma or carcinoma a thymus carcinoma or an ovarian arrhenoblastoma one constant change was invariably present—namely degranulization and hyalinization of the basophil cells The normal cytoplasm charged with ripe basophil granules is replaced by a dense homogenous hyaline cytoplasm This may be complete or partial and vacuolization may occur Crooke postulates that such a hyaline change does not appear to be an expression of cell degeneration in the ordinary sense but is probably an expression of altered physiological activity producing the symptomatology of Cushing s syndrome as distinct from that of virilism

I have frequently pointed out however that such a change in the pituitary gland may well be secondary since when Cushing s syndrome is associated with an adrenal tumour the removal of the latter abolishes the symptomatology Further the changes described by Crooke are similar to if not identical with the changes in the basophil cells occurring after the injection of oestrone testosterone &c It therefore may well be produced by the excess of oestrogens and/or androgens secreted by an adrenal cortical tumour Further the sex organs and functions in Cushing s syndrome are involuted and diminished respectively so that one might well conclude that the gonadotrophic function of the hyalinized basophil cells must be decreased Such cells however may be responsible for adiposity hypertension diabetes and other features of the syndrome although there is considerable evidence that the hormones of the adrenal cortex can produce these three major

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and stall and exercise a local effect presumably on the diencephalic nuclei in whose neighbourhood the veins appear to disgorge their product To such a neurotrophic effect may be ascribed the adiposity the hypertension and possibly the glycosuria

The fact that a chromophobe adenoma may occasionally be associated with Cushing s syndrome (Fuller and Russell 1936) or that a basophil adenoma (Close 1934 Susman 1935) or even hyalinization of the basophil cells (Ecker 1938) may be found in a small percentage of post mortems on non endocrine patients does not in my opinion obviate more positive evidence as to the significance of the basophil cells in Cushing s syndrome whether the changes be primary or secondary Crooke s histological findings have been thoroughly confirmed by Rasmussen (1938) who noted as significant the additional features of ballooning of the nucleus excessive vacuolization and a tendency to multinucleation Ecker states that these latter changes were not found in a single one of 721 cases of non endocrine disease McLetchie (1944) while confirming the findings of Crooke suggested that the abnormalities of size and vacuolization in the basophil cells represent a phase of reaction to hypogonadism and are only of secondary importance in the morbid process of basophilism also that basophil cell hyperactivity is the essential abnormality of Cushing s syndrome and that basophil cell hyalinization is a cytoplasmic change resulting from hyperactivity

Other Endocrine Glands

Ovary (*a*) *Tumours* Apart from the fact that an adrenal cortex rest may be displaced to the ovary and from there give rise to a virilizing tumour virilism may also occur from an ovarian arrhenoblastoma The virilism may be complicated by the other features of Cushing s syndrome e g adiposity hypertension and diabetes and in such cases hyalinization of the pituitary basophil cells has been found together with apparently normal adrenals (Canelo and Lisser 1939) The histopathology of arrhenoblastomas is discussed in the Adrenal section p 169 (*b*) *Ovarian atrophy* Whatever the primary cause of Cushing s syndrome may be the ovaries usually show secondary changes of atrophy or involution Thus Cushing (1933)

features by themselves The summation of clinical and experimental evidence suggests that both the pituitary and the adrenal cortex play a contributory role in such symptomatology, and the importance of the pituitary (quite apart from its adrenocorticotrophic function) is indicated by (1) the production of many features of Cushing's syndrome in puppies by the injection of extracts of anterior pituitary gland (Thompson and Cushing 1934) (2) the occurrence of adiposity and diabetes and possibly hypertension in pituitary or hypothalamic pituitary disorders uncomplicated by adrenal involvement (3) the cure of Cushing's syndrome by deep radiation of or radon seeds implanted in the anterior pituitary gland

It is interesting to note that the hyalinization changes of Crooke do not involve the cells of the actual basophil adenoma but rather the basophil cells in the rest of the gland The significance of a basophil adenoma as one of the initiating causes of Cushing's syndrome is reinforced by the reporting of one case in which the lesion was malignant namely a basophil carcinoma (Cohen and Dibble 1936)

Heinbecker (1944) has drawn attention to the hypothalamus as being the site of the primary lesion in some cases of Cushing's syndrome Thus he found that in dogs an experimental lesion of the hypothalamus (paraventricular nuclei) produced a marked loss of basophil cells and degenerative changes in the remaining basophil cells resulting in adiposity gonadal involution and polyuria He found histological changes in the paraventricular nuclei of four cases of Cushing's syndrome in which the adrenal glands were not obviously involved and degranulization of the basophil cells comparable to that found in his dogs There were no such changes in the hypothalamus of one patient with Cushing's syndrome in which an adrenal tumour was present Heinbecker suggests that a basophil adenoma may be an attempt to compensate for the depression of basophil function In connexion with Heinbecker's work on the hypothalamus it is interesting to note that in two neurological cases Barker and Craig (1936) found a lesion of the floor of the third ventricle associated with plethora and polycythaemia two features of Cushing's syndrome Cushing (1933) considered that the hypothalamus might be influenced by the pituitary gland Thus, he observed that the basophil cells may invade the posterior lobe

and stalk and exercise a local effect, presumably on the diencephalic nuclei in whose neighbourhood the veins appear to disgorge their product To such a neurotrophic effect may be ascribed the adiposity the hypertension and possibly the glycosuria

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recorded senile fibrotic or atretic ovaries, atretic follicles with no corpora lutea, numerous follicular cysts of variable size and normal germinal epithelium but no primordial ova, follicular stimulation without ovulation and luteinization. Such changes are characteristic but occasionally normal ovaries and normal corpora lutea are found (Swan and Stephenson, 1935).

Testes. Atrophy of the spermatogeneous epithelium and of the interstitial cells with fibrosis is the usual finding, but normal testes have been recorded.

Thymus. In two males Cushing's syndrome was thought to be due to a carcinoma of the thymus, the adrenals however being large and the basophil cells showing hyalinization (Leyton, Turnbull and Bratton, 1931). In the majority of cases, however, the thymus gland has been atrophic or completely replaced by fat. In some it has been normal, and in one boy of 19 the thymus was found to be enormous, the adrenals long, thin and hypoplastic, and the testes atrophic. A basophil adenoma was present in the pituitary (Freyberg, 1936).

Thyroid. The thyroid gland is frequently found to be slightly enlarged at autopsy, with, however, flattened cuboidal epithelial and colloid in the vesicles. It has the appearance of a resting gland, and not a hyperplastic one. Sometimes the thyroid is normal, or small, or fibrotic.

Parathyroids. These may be normal or fibrotic or infiltrated with fat. Occasionally an adenoma may be present, but there was no evidence of hyperplasia or neoplasm in one case showing a marked increase in calcium excretion and a negative calcium balance (Albright, 1938).

Pancreas. No constant findings have been recorded, and although fatty degeneration of the islets may occur, the pancreas is more usually normal, even in the presence of gross diabetes.

Other Organs

The kidneys may be normal or may show histological evidence of chronic nephritis, and sometimes the cardiovascular and renal lesions are identical with those of malignant nephrosclerosis (MacMahon, Close and Hass, 1934). Minute deposits of calcium may be found in the kidney substances and the calyces as in hyperparathyroidism. With or without renal lesions, cardiac hypertrophy and arteriosclerosis are not infrequent findings.

as might be expected from the fact that hypertension is a common symptom

Clinical Picture

Cushing's syndrome usually manifests itself in the second or third decade of life with a dramatic increase in weight due to accumulation of fat a plethoric appearance of the face amenorrhoea and hirsuties in the female impotence in the male and other characteristics of a rich symptomatology described below Occasionally it occurs at puberty and a few cases have been described in young children e g aged 6 The latter are associated with an adrenal tumour and will be considered under Sexual Precocity The syndrome occurs in both sexes but is more frequent in women Cushing found that pregnancy immediately preceded the onset of the syndrome in 5 of the 9 married women in his series of 11 women

Adiposity The fat tends to be deposited in the regions of the face and neck breasts abdomen and thighs the extremities being spared and often being graceful and well shaped In some cases fat is actually lost from the thighs and upper arms and concentrated on the abdomen and face The adiposity is occasionally painful A disturbance of fat metabolism is also indicated by high concentrations of blood cholesterol massive adipose deposition in the viscera and the liver the concentration of hepatic fatty acids being recorded as high as 35 mg per cent compared with the normal 5 mg per cent (Lukens 1937 Ingle 1943) Although as in other forms of adiposity there may be an excessive caloric intake this explanation in itself is inadequate Albright (1941) explains the obesity of Cushing's syndrome as a hypergluconeogenesis from protein with conversion to and storage as fat and caused by an increase in the secretion of the C_{11} oxygenated steroids of the adrenal cortex Cushing considered that the basophil cells invaded the posterior pituitary and discharged their products into the hypothalamic nuclei thus causing adiposity and hypertension The adrenal cortex is implicated by Verzar (quoted by Ingle 1943) who noted a decrease in fat absorption after adrenalectomy and a failure of phosphorous to produce fatty livers in adrenalectomized animals

The lineae distensae which occur in all forms of adiposity

recorded senile fibrotic or atretic ovaries atretic follicles with no corpora lutea numerous follicular cysts of variable size and normal germinal epithelium but no primordial ova follicular stimulation without ovulation and luteinization Such changes are characteristic but occasionally normal ovaries and normal corpora lutea are found (Swan and Stephenson 1935)

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the physiognomy from the pallid adiposity of other pituitary adiposities The cause of this as of the dusky red of the lineae distensae is not really known since it may occur in the absence as well as in the presence, of polycythaemia

Hirsuties In women hair appears on the face and body as described under Virilism This hirsuties must be ascribed to the excessive secretion of androgens by hyperplastic or neoplastic adrenals because there is no known pituitary hormone which can directly produce hirsuties the pituitary adrenotrophic hormone acting through the adrenal glands The hairiness may however be only slight in degree although it takes on a masculine pattern Sometimes hairiness is considerable on the face and limbs but absent from the body suggesting that no hair follicles are present in that region or that they are incapable of responding to the androgenic stimulus The hair *of the head in women tends to fall out* Hypertrichosis may occur in male adolescents or boys but sometimes facial hair fails to develop or becomes less in the adult

Hypogonadism Amenorrhoea is the rule in women Occasionally menstruation is present but scanty and in some cases menstruation may be normal Swan and Stephenson (1935) recorded normal menstruation in a woman of 31 after which there was a period of amenorrhoea followed by a resumption of normal menstruation on the giving of thyroid In this case the ovaries were normal at autopsy more usually the ovaries are found to be atrophic or involuted or show cystic degeneration The uterus is usually infantile and the endometrium thin and atrophic

In the male involution or failure of development of the sex organs and an absence of potency is the rule In Josephson's case (1936) of a boy of 17 the clinical diagnosis was at first Fröhlich's syndrome but plethora hypertension red lineae distensae and osteoporosis led to the proper diagnosis of Cushing's syndrome Hypogonadism probably results from failure of secretion of pituitary gonadotrophins which may be associated with a primary pituitary dysfunction or secondary suppression of gonadotrophic hormone secretion in the presence of excessive secretion of androgens or oestrogens by the adrenal cortex The absence of a pituitary gonadotrophic stimulus is difficult to explain in those cases where a basophil adenoma has

may be especially well marked in Cushing's syndrome especially on the breasts axillae and lower abdomen and they are more obvious since they are a dusky red or purple colour and not



(a) (b)

FIG 30 CUSHING'S SYNDROME Female basophilism amenorrhoea acute plethoric obesity with hypertrichosis Spinal kyphosis from skeletal decalcification Vascular hypertension Polycythaemia Duration 7 years Autopsy (a) The patient aged 20 and (b) 5 years later (1913) at the height of the disorder Described by Dr Turney *Proc Roy Soc Med* (Section *Neurol and Ophth*) 1913 vi 69

white as is usual in Fröhlich's syndrome or familial pituitary adiposity Such a coloration however is in my experience not limited to Cushing's syndrome and may occur in the absence of other features which make such a diagnosis justifiable

Plethora A congested well coloured plethoric countenance is quite characteristic of Cushing's syndrome and differentiates

thyroidism Evidence of renal disease may not be present in life or may only be found on special examinations e g granular casts in the urine and poor renal function tests In some cases however as in that of Close (1935), there may be frequency haematuria blurring of vision vomiting cramps dyspnoea drowsiness and anuria as well as albuminuric retinitis and intractable headaches

Psychoneurotic symptoms Neurosis or mental depression is sometimes met with and Schlezinger and Horwitz (1940) recorded a case which came to autopsy and in which there was a depressive psychosis and an extrapyramidal neurological disorder Many endocrine disorders are associated in a small percentage of cases with neuroses or psychoses and since the cure of the endocrinopathy frequently results in the cure of the psychiatric condition one must conclude that the association is not merely coincidental

Skeletal changes The bones tend to become rarefied and soft Clinically this is shown by kyphosis and bent shoulders with resulting lessening of height Radiographically the vertebrae are seen to be compressed and all the bones of the body rarefied compared with controls Backache in the lumbo sacral region is not uncommon and may be due to compression or spontaneous fracture of vertebrae (fig 31(*b*)) as also occurs in ribs clavicles and long bones This clinical picture is quite comparable to that of hyperparathyroidism but although an increased calcium excretion in the urine has been demonstrated (Albright) values for serum calcium phosphorus and even phosphatase are usually normal Further the parathyroid glands in most cases are histologically normal but fatty infiltration slight hyperplasia and in one case adenoma have been reported A further analogy with hyperparathyroidism are the fine deposits of calcium which sometimes are found throughout the kidneys or minute brown calculi in the calyces and secondary chronic nephritis with sclerosed glomeruli and calcium deposits as in Case P 4211 of Cushing (1933)

Apart from rarefaction and softening of the bones with resulting round shoulders, Cushing observes that nearly all the females appear to have been definitely undersized although this was by no means true of the males some of whom were even tall

been found unless we regard this adenoma as an attempt to compensate for the degranulization and hyalinization of the other basophil cells In any case no one has demonstrated any excess of gonadotrophic hormone in the blood or urine of patients with Cushing's syndrome

The blood Although plethora is almost constant polycythaemia is found in less than 50 per cent of patients Cushing recorded a polymorphonuclear leucocytosis in some patients which appears to be the opposite of the relative lymphocytosis of Addison's disease

There is a tendency to subcutaneous haemorrhages either spontaneous or on slight trauma When these occur on the anterior aspects of the legs or where there is some patchy cyanotic discoloration in this area a characteristic pattern resembling marble results and is given the name cutis marmorata

Hypertension and the kidneys High blood pressure systolic and diastolic (e g 220 and 140 respectively) is a frequent finding in Cushing's syndrome It may occur in the absence of clinical or pathological renal disease (Lyall 1935) or in association with chronic nephritis (Cushing and others) or malignant nephrosclerosis (MacMahon Close and Hass 1934) The cause of the hypertension is probably both pituitary and adrenal It might be ascribed to an increase or change in the basophil cells since invasion of the posterior lobe of the pituitary by basophil cells was found by Cushing in eclampsia and also since low blood pressure is found in Addison's disease where there is a diminution in the number of pituitary basophil cells However the suprarenal cortex is also involved aetiologically since in Addison's disease the adrenal cortex may be destroyed and the medulla intact and because adrenaline free cortical extracts or synthetic desoxycortone will in time produce a normal or supernormal blood pressure in such patients Further the removal of an adrenal cortical tumour in *Cushing's syndrome* will result in a fall of blood pressure to normal

The kidneys are probably involved as secondary to arterosclerotic or endarteritic changes although this explanation is not an adequate explanation of the rare complication of malignant nephrosclerosis In some patients the renal changes are due to minute depositions of calcium throughout the kidney substance, and in the tubules as may occur in hyperpara



Fig 31 (b)

(b) Same case X ray of spine showing decalcification and compression fracture

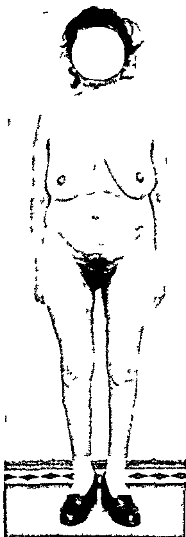


FIG 31 (a)

FIG 31 CUSHING S SYNDROME (a) Patient aged 51 (1946) in 1943 hairiness of face backache and increase in abdominal fat hypertension discovered In 1946 X rays showed rarefaction of skeleton and undetected fractures of ischium lumbar spine and ribs also slight enlargement of sella turcica Blood pressure 250/150 diabetic sugar tolerance curve blood cholesterol 260 mg increased fat on abdomen and face decrease of fat on whole length of arms and legs so that total weight hardly changed

are hyperplastic or neoplastic and some of the multiple functions of the adrenal cortex are overactive However a comparable condition is found in the adrenogenital syndrome and the above thesis is supported by the fact that in both disorders some pigmentation of the orbits face and neck may be found In some phases of the disorder however there may be evidence of hypofunction of all parts of the adrenal cortex with increased strength and high serum sodium concentrations

Climacteric type of Cushing s syndrome Archard and Thiers (1921) described the syndrome in a woman of 71 Menstruation had been normal throughout life she had married at 37 years of age and had a son the next year after which her husband left her At the age of 69 she fractured a leg and glycosuria was discovered as well as hypertension systolic 220 and diastolic 100 mm of Hg However he records that hair on the chin commenced to grow at the age of 9 years and that the patient had shaved intermittently My own patient had regular but scanty menstruation throughout life and two children She developed her symptoms at the age of 47 after menstruation had ceased (see appendix of cases)

Diagnosis

The clinical diagnosis of a typical case is easy according to definition Many mild and incomplete forms however will be met with and in other cases when the patient is first seen the proper diagnosis may be adrenogenital syndrome but in the course of time further symptoms develop which justify a change of nomenclature to Cushing s syndrome The gross cause of the syndrome is not always obvious An adrenal tumour might be indicated by radiography after uroselectan by a high excretion of 17 ketosteroids or more important of C_{11} glycogen steroids in the urine Evidence of a basophil adenoma or of changes in the basophil cells is rarely forthcoming clinically but in the absence of an adrenal or ovarian tumour both must be suspected An ovarian tumour is usually revealed by pelvic examination under anaesthetic but not always Rarely a thymus carcinoma may be the gross lesion and it may be shown in a radiogram of the chest

Course and Prognosis

The average duration of life in Cushing s series was five years

Thyroid The thyroid gland is frequently enlarged in smooth bilateral fashion which clinically suggests a colloid gland This is in keeping with the histological picture of cuboidal (sometimes low and flattened) epithelium lining vesicles containing colloid The basal metabolism is occasionally raised but more usually it is normal or subnormal Some degree of exophthalmos is not uncommon but it is evidently independent of thyrotoxicosis It might be ascribed to a direct hypothalamic stimulus or to a pituitary thyrotrophic one on the assumption that the thyroid gland itself in these cases is refractory to such a stimulus Transient diplopia slight papilloedema and retinal exudates are met with and are probably associated with hypertension

Diabetes mellitus Hyperglycaemia and glycosuria with symptoms and complications of diabetes mellitus arise in some 50 per cent of cases and even in the remainder a delayed fall in the carbohydrate tolerance curve is the usual finding Occasionally diabetes is the presenting feature and in one case (Sprague 1943) it was the only manifestation of an adrenal cortical tumour As in acromegaly the diabetes is only slowly progressive and rarely the cause of death it may be relatively refractory to insulin its course and degree tend to follow that of the major syndrome diminishing with remission natural or induced by treatment and disappearing when the fundamental cause of the disorder has been removed It seems probable that both the anterior pituitary and the adrenal cortex play a part in the production of diabetes associated with Cushing's syndrome The role of the adrenal corticosterones has been fully discussed and the pituitary may act not only by virtue of its corticotrophic hormone but also through its diabetogenic hormone which is effective even in the absence of the adrenals and its anti insulin hormone The polyuria and polydipsia which are not infrequently features of Cushing's syndrome may be due to glycosuria but also occur in its absence when they might be ascribed either to the increased calcium excretion or possibly to the invasion of the posterior pituitary gland by basophil cells

Other features Fatiguability weakness and susceptibility to infection may be ascribed to a paradoxical diminished function of the adrenal glands paradoxical in the sense that the adrenals

are hyperplastic or neoplastic and some of the multiple functions of the adrenal cortex are overactive However a comparable condition is found in the adrenogenital syndrome and the above thesis is supported by the fact that in both disorders some pigmentation of the orbits face and neck may be found In some phases of the disorder however there may be evidence of hyperfunction of all parts of the adrenal cortex with increased strength and high serum sodium concentrations

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Course and Prognosis

The average duration of life in Cushing s series was five years

The patients become gradually weaker and easily fatigued They also develop a susceptibility to infections particularly staphylococcal and multiple boils carbuncles and ischiorectal abscess broncho pneumonia and meningitis may precipitate death Some cases are however much more chronic and spontaneous remissions may occur

Treatment

An adrenal tumour if present should be removed and cortical extract given before and after operation as the latter may be followed by severe adrenal insufficiency until the opposite adrenal undergoes compensatory hypertrophy An ovarian arrhenoblastoma should also be removed surgically and a thymus tumour radiated In the absence of such gross lesions, deep radiation of the pituitary gland is indicated Lawrence (1934) recorded a dramatic cure by such treatment in a woman of 37 showing the characteristic syndrome Obesity disappeared blood pressure returned to normal diabetes cleared up completely and both hirsuties and osteoporosis were considerably ameliorated Cushing himself had an excellent result in a male of 30 treated with deep radiation and the writer has seen similar striking benefit However this is not always the case and Pattison and Swan after deep radiation had failed produced a cure in two patients by inserting radon seeds into the sella turcica by open operation Dunn used large doses of oestradiol 10 000 to 50 000 units three times a week over periods of 1 to 4 years often considerably ameliorating the plethora adiposity hypertension and hypertrichosis as well as the genital dystrophy Gill however failed to find any benefit from such therapy except of headaches and lassitude Testosterone has been used to increase strength but has the disadvantage of producing or aggravating pre existing acne and it is difficult to appreciate its rationale in the presence of high androgen excretion

Examples of Cushing's Syndrome (in the Female)

Case 1 Dr D C Hare's case 1935 This case in a woman of 33 came under the personal observation of the writer at the request of Dr Hare and is of classical interest It was the first example of Cushing's syndrome due to carcinoma of the suprarenal gland in which a high excess of urinary androgens was discovered (Simpson de Fremery and

Macbeth) and it was the first pituitary gland in which Crooke found the characteristic changes in the basophil cells In view of Cushing's aetiological theories of his syndrome the existence in this case of an adrenal carcinoma and Crooke's expert knowledge of the histopathology of the pituitary gland I ventured to urge Dr Hare to send the pituitary gland to Dr Crooke for special examination

The woman was unmarried of normal build and with regular menstruation until the age of 31 when oligomenorrhoea and then amenorrhoea set in At the same time there developed adiposity blotchy complexion severe headaches hirsuties in the facial region and slightly on the trunk and loss of scalp hair There was slight enlargement of the clitoris Later there followed plethora polycythaemia hypertensions kyphosis and a diabetic tolerance curve with intermittent traces of glycosuria Urinary androgens were more than 400 capon units per litre (normal less than 50) and the urinary oestrogens were also high greater than 600 units per litre There was no excess of gonadotrophic hormone The patient died a few hours after operation There was a large carcinoma of the left suprarenal gland and the cortex of the right was a quarter of the normal thickness The percentage and distribution of basophil cells were normal and there was no basophil adenoma but the basophil cells showed hyaline changes (Crooke) The ovaries were atrophic and consisted of dense fibrous tissues with some corpora albicantia

Case 2 Dr H G Turney's case 1913 After passing a tribute to Cushing's monumental work on the pituitary gland Turney described this case

Miss A O aged 25 was completely normal until the age of 17 when menstruation ceased she began to put on weight and she experienced severe pain in the back which became bent (Fig 30) the kyphosis causing an apparent decrease in height from 62 to 59½ inches A spontaneous fracture of the sternum occurred On examination Turney observed plethora red abdominal lineae distensae scanty pubic hair bruising of limbs on slight pressure dry skin hypertension and polycythaemia Sugar tolerance appeared normal Dr Dixon found a pressor substance in the urine Turney considered that the condition was due to a pituitary adrenal abnormality Dr Parkes Weber (1926) later reported on this same case the patient having several spontaneous fractures and multiple abscesses At autopsy there was found an enlarged left suprarenal gland with bulky cortex an apparently normal pituitary gland soft decalcified bones atrophic ovaries and chronic nephritis

Case 3 Cushing's case No 14 1932 This case illustrates how Cushing's syndrome in a girl may be initiated by sexual precocity which gives place to amenorrhoea At the age of 8 Alice developed a voracious appetite and adiposity At the age of 10 she menstruated and developed secondary sexual characteristics At 13 menstruation ceased entirely and she developed hypertrichosis plethora acrocyanosis purplish abdominal striae hypertension convulsions rarefaction of bones and a diabetic type of sugar tolerance curve Deep radiation of the pituitary gland produced considerable improvement in all features

Examples of Cushing's Syndrome (in the Male)

Case 4 Dr Raab's case (1924) quoted by Cushing 1932 A tall man of 31 with well developed genitalia and normal masculine hair distribution developed headaches adiposity and impotence Long dark red lineae distensae were conspicuous on the lower half of a protuberant fatty abdomen Additional features were pain in the lower back and a fatal streptococcal infection of the hand Autopsy showed enlargement of the pituitary gland and a basophil adenoma of the pars intermedia invading the posterior pituitary gland The adrenals showed no gross change The testes were strikingly small there was an absence of spermatogenesis and the interstitial cells were diminished

Case 5 Dr McLetchie's case (1944) This was a male aged 32 admitted to hospital with cellulitis of the left foot For two years he had been unwell his hair had become grey he had put on weight and fat libido had disappeared his facial hair grew slowly shaving only being necessary twice weekly instead of daily and diabetes had been present during the past year On examination he was florid adipose with bluish red abdominal striae had hypertension (170/100) glycosuria ketonuria and polyuria He died in coma after broncho pneumonia had developed At autopsy the pituitary basophil cells showed hyalinization and vacuolization the adrenals were apparently normal the pancreas embedded in fat but not abnormal the testes were small but of normal appearance the latter being unusual as atrophy or involution is more characteristic and impotence was present in this case

Case 6 Dr Freyberg's case (1936) A male aged 19 after a normal childhood began to put on weight rapidly at the age of 12 Growth in stature ceased at the age of 15 and was only 5 feet Although he had erections and seminal emissions from the age of 13 to 15 his voice remained high pitched and he never shaved having only soft down on the face After 15 erections ceased and he complained of impotence and lack of libido The testes were small Plethora and hypertension were present and demineralization of the skeleton There was also delayed union of the epiphyses Sugar tolerance was normal Roentgen therapy was ineffective He died after abdominal laparotomy Autopsy revealed a basophil adenoma of the anterior pituitary gland thin hypoplastic cortex in both adrenal glands a huge thymus small testicles in a pre adolescent stage of development and complete aspermogenesis

Unusual Types of Cushing's Syndrome

The following two examples came under the observation of the writer and were demonstrated at a clinical meeting of the Medical Society of London (Simpson 1936)

Case 1 Chronic Cushing's syndrome with regular menstruation S R a female aged 51 suffered from diabetes mellitus hypertension adiposity polycythaemia plethora hirsuties of face and loss of hair of head Menstruation started at the age of 12 had always been regular

of 2 or 3 days duration but rather scanty Menstruation ceased 8 months previously The patient married at the age of 21 but had never b come pregnant As a girl and adolescent the patient was very thin but in the first year of marriage her weight increased by 3 stones and



FIG 3 Author ca e I p 11 Fat beard d diabetic woman with hyperten sion plethora polycythaemia abdominal lineae d stensae an l loss of scalp hair This syndrome was described by Achard and Thiers Parkes Weber and Cushing

had b en increasing gradually ever since up to a maximum of 17 stones in 1932 There was then some loss of weight without dieting probably due to the onset of diabetes mellitus During the past ten years she had developed a beard and moustache and the hair of the head had fallen out e pecially in the frontal region producing symmetrical angular re traction of hair edge as in the male She came under medical observation

in 1933 The blood pressure was 220/110 The urine contained some albumen and glucose Carbohydrate tolerance was diminished fasting blood sugar 178 mg 50 gm glucose 30 minutes after 192 mg 60 minutes after 218 mg 90 minutes after 221 mg 120 minutes after 272 mg per cent The plethoric countenance was associated with gross polycythaemia red cells 6 540 000 haemoglobin 125 per cent There were white lineae distensae on the abdomen and no hair along the linea alba There was a marked tendency to bruising but no gross discoloration of the legs Kyphosis was slight The clitoris was not enlarged The interest of this case lies in the persistence of menstruation throughout life and the gradual development of the syndrome probably over a period of 30 years with exacerbation for 10 years marked with the development of the menopause

Case 2 Climacteric Cushing s syndrome This patient aged 47 had had 10 pregnancies consisting of 5 premature babies who did not survive 1 ectopic 2 miscarriages and 2 children aged 10 and 2? Menstruation commenced at 14 occurred at intervals of 28 days but was always scanty in amount and lasted no more than 2 days in the past year the menopause had been indicated by prolongation of the intermenstrual period At the age of 40 she was known to have weighed 11 stones 8 lb to have had a normal blood pressure of 120/70 a normal blood count and a normal urine At the age of 47 she weighed 15 stones 4 lb had a hypertension of 190/100 a polycythaemia of 6 100 000 red cells and haemoglobin 115 per cent and glycosuria The latter was associated with a diabetic tolerance curve fasting blood sugar 199 mg 50 gm glucose 30 minutes later 199 mg 60 minutes 215 mg 90 minutes 194 mg 120 minutes 140 mg and 150 minutes 130 mg per cent Additional features were a plethoric countenance cyanotic patches on the legs with subcutaneous haemorrhages and a tendency to bruise very easily and hair was present on the chin and lips and along the linea alba and the hair of the head had fallen out considerably in the last few months There were no well marked lineae distensae and no gross kyphosis Pelvic examination showed no abnormality (Dr G Dearnley)

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CHAPTER XI

ADIPOSITY

THIS is a subject which according to some is no problem at all all fat people being gluttons and according to others still remains a complete enigma Some of the glutton protagonists admit that there is such a thing as pathological hunger , and others recognize that some people with enormous appetites remain thin An explanation given for this apparent anomaly is that they expend enormous energy whereas the fat ones expend little energy Those who consider these explanations too facile find themselves in the dilemma of concluding that adipose people defy the physical laws of energy namely a balance between intake and output or admitting that the methods of measurement and calculation and knowledge of intermediate biochemical processes remain beyond complete comprehension at the moment

As to aetiological factors the endocrines are rejected entirely by some but inculpated by others The hypothalamus is being given increasing importance and has led some to reject entirely the pituitary as an aetiological factor Whatever the aetiology the mechanism and physiochemical problems still remain to be solved As for myself I do not believe we have yet reached a stage of knowledge at which we can be dogmatic about the cause or mechanism of adiposity or an equally important problem leanness or inability to store fat Some ten years ago at a discussion on adiposity at the Royal Society of Medicine when the glutton theory was being strongly supported I ventured to state that it was as inadequate to attempt to explain adiposity by excessive food intake as it would be to ' explain the polyuria of diabetes insipidus by excessive fluid intake' This epigrammatic statement does not carry us far, but it gives us pause to think and challenge intellectual complacency about a very complex subject

I am not attempting the solution of the cause of adiposity in this chapter but rather putting forward a few fundamental experimental and clinical facts and theories If my contribution has any propensities it is (1) to re establish the importance of

the endocrine glands particularly the pituitary (2) to repeat with further considerations the theory put forward in the 1938 edition of this book namely that adiposity is generally due to hyperactivity of the endocrine glands and not as is generally held to insufficient activity and (3) that inherited genetic factors determine the majority of cases of adiposity although they often operate through a genetically determined disposition or activity of endocrine glands

Experimental and Physiological Evidence

(1) *Hypothalamus* Many experimentalists have placed beyond dispute the fact that adiposity apparently produced by hypophysectomy is due to simultaneous injury of the hypothalamus (Smith 1930 Bailey and Bremer 1921) and that uncomplicated hypophysectomy leads to loss of weight and loss of fat Heinbecker and White (1942) defined the lesion as being a bilateral one in the posterior hypothalamus caudal to the paraventricular nuclei Brooks Lambert and Bard (1942) produced hypothalamic lesions in mature monkeys and noticed that they doubled their weight in 9 months after which the weights remained relatively constant The presence or absence of an associated diabetes insipidus or hypogonadism did not influence the development of the adiposity When deprived of food the adipose monkeys lost weight but not so rapidly as the control monkeys Most of the operated monkeys ate a great deal more than their controls Some of the animals became obese without eating more than the controls However all the operated monkeys were much less active than the controls In rats Brooks and colleagues (1942) found that a hypothalamic lesion increased the maximum weight of an eaten meal from 4 gm to 20 gm When paired fed with controls only one out of ten operated animals gained more weight than the controls There was no difference in the respiratory quotient of operated and controlled animals (Long et al 1942)

In view of the close relationship between the hypothalamus and the pituitary it would seem possible that such hypothalamic lesions acted via the pituitary gland Such is not the case for (1) the histology of the pituitary is normal and (2) complete hypophysectomy a few days after the hypothalamic lesion in rats does not prevent or lessen the adiposity which develops

3 to 6 weeks after the hypothalamic operation (Hetherington and Ranson 1942) It is necessary therefore to accept the fundamental and unequivocal evidence in support of the view that a certain hypothalamic lesion results in adiposity without intervention of the pituitary gland and that the mechanism appears to be excessive appetite and food intake As a complication of clinical interest Long and colleagues found albuminuria often with casts in 13 of 15 obese rats 12 weeks after they became obese and 4 of these showed striking histological changes in the glomeruli and tubules

(2) *Pituitary gland* Hypophysectomized animals in the absence of an associated hypothalamic lesion lose their body fat Anyone reading the original papers of Evans (1923) describing the growth promoting properties of his anterior pituitary extracts will be struck by the enormous adiposity of the injected rats compared with the controls Evans was mainly interested in the accelerated skeletal growth but he does refer with photographs to this coincidental adiposity Regardless of whether other hormones e g cortico adrenotrophic or pancreatotrophic &c were present in Evans s crude extracts his experiments furnish evidence of the production of adiposity by an extract of an endocrine gland The only other endocrine change recorded by Evans is the formation of corpora lutea

Young (1941 and 1945) found that when young puppies were treated daily for long periods with diabetogenic pituitary extract they did not exhibit glycosuria as did adult dogs but rapidly increased in body weight like the animals in the classic experiments of Evans However nitrogen and water retention and an increase of protein tissue were observed and the relative percentage of fat decreased although the puppies and rats looked fat and well nourished After many months of treatment diabetes did ultimately develop in some of the puppies and thereafter the pituitary extract lost its growth promoting action and merely exerted a diabetogenic action [Young (1944) also refers to the later work of Evans and colleagues in which they showed that the administration of purified growth hormone preparations to partially depancreatized rats led to an increase in glycosuria]

Ketones are an intermediate product of fat metabolism Their presence in detectable form in the blood or urine is usually

interpreted as due to an excessive rate of breakdown of endogenous or exogenous fat—too fast for their complete catabolism Burn and Ling (1928, 1930) found that injections of an alkaline extract of anterior pituitary gland produced ketonuria in the rat and that posterior pituitary extract decreased this ketonuria and caused a disappearance of glycogen from the liver (1929) Neufeld and Collip (1939) found that this ketonaemia action was associated with an infiltration or deposition of fat in the liver (the latter is also produced by posterior pituitary extracts) In 48 hour fasted animals the fatty infiltration of the liver produced by anterior pituitary ketogenic hormones was associated *with a decrease in the total fat of the rat s body* Soskin and Levine (1941) showed a striking lack of ketosis in hypophysectomized animals

O Donovan and Collip (1938) claimed to have prepared a specific metabolic principle of the pituitary closely related to the melanophore hormone and because of the lowering of the respiratory quotient suggested that it stimulated fat metabolism Further work in this direction is awaited with considerable interest because of its potential clinical application

The water retention action of posterior pituitary extracts is of course well known and has to be considered as a possible factor in adiposity associated with water retention

(3) *Adrenal cortex* Adrenalectomized animals tend to lose *their body fat and this can be prevented by a potent cortical* extract (see Adrenal section) There is however no consistent change in the blood lipoids of adrenalectomized animals Adrenalectomy will prevent the fatty infiltration of the liver that usually follows phosphorus administration injections of anterior pituitary extracts or over feeding Adrenalectomy also abolishes the ketonuria produced by depancreatization or phloridzin diabetes (Ingle 1943) Adrenalectomized animals have a high respiratory quotient It is difficult to harmonize these facts with the loss of body fat

The corticosterone diabetogenic group of adrenal cortex hormones produce a loss rather than a gain of weight in the experimental animal (Ingle 1943 1944) Nevertheless Albright (1943) *explains the adiposity associated with adrenal tumours* as due to hyperglucogenesis from protein by corticosterone and subsequent conversion of the glucose to fat

(4) *The gonads* In the section dealing with the gonads we have seen that castration does not necessarily produce adiposity and in some species may produce an inability to put on fat or loss of weight (Conn 1944) Where adiposity is produced, it might be explained by the hypertrophy of the anterior pituitary and the adrenal cortex that follows castration

The greater tendency of women to adiposity is a clinical impression Zondek and Mark (1939) found that oestrogens produce concurrent calcaemia and lipaemia in the fowl This has been confirmed by many observer in other birds Riddle (1942) found that at each period of egg production in the pigeon, the serum fat less phosphatides increases from about 470 mg per cent to a maximum of about 2 900 mg per cent at 60 hours preceding the ovulation of the first egg These birds produce high oestrogen secretion at each cycle and the effect can be produced by pregnant mare s serum

(5) *Pancreas* In uncontrolled diabetes either in man (Bloor 1921) or in depancreatized dogs (Gibbs and Chaikoff, 1941) the blood lipoids increase The latter observers found that the increase was mainly in fatty acids and less marked in phospholipids or cholesterol Insulin will correct these abnormalities although its effect on the blood lipoids of normal animals is less certain Insulin will also prevent or correct the fatty infiltration of the liver in depancreatized animals

Insulin administration will produce obesity in animals if chronic hypoglycaemia is maintained and this obesity is associated with an increased appetite and increased food intake (Barnes and Keeton 1940) The theory that insulin converts carbohydrate to fat has been put forward several times Recently Wertheimer (1945) has thrown fresh light on the subject by showing that insulin produces glycogen in fat tissue before the latter is increased by further fat deposition This glycogen can be detected histologically and by chemical analysis and is most probably an intermediate step in the deposition of fat formed from carbohydrates

(6) *Genetics* Danforth (1937) has shown that in a strain of yellow mice there occurs a pronounced form of adiposity more marked in females which is associated in cross breeding experiments with the yellow colour Both the yellow colour and the adiposity are genetically determined These animals lay on

much more fat than control mice on the same diet and this fat can be utilized when required by fasting

A tendency to acquire enormous fatty depositions in the autumn and to utilize them in the winter is seen in animals who hibernate or semi hibernate e g the dormouse and badger

(7) *Thyroid* Thyroxine produces catabolism by raising the rate of metabolism of all food and tissues but its predominant action is on protein metabolism (see Thyroid section)

Summary Adiposity can be genetically determined and the female sex may then be more severely affected Hypothalamic lesions may produce adiposity without any apparent evidence of secondary endocrine disturbance The pituitary the adrenal cortex and the pancreas may by over activity produce adiposity and their removal cause a loss of fatty tissue The gonads have a less certain and probably more indirect effect on fat metabolism Certain pituitary extracts produce ketosis and possibly a catabolic effect on adipose tissue Adrenal corticosterone and allied substances may cause a loss of weight under certain conditions Thyroid is a general accelerator of metabolism with a predominant action on proteins

As regards mechanism increased appetite and food intake usually but not invariably precede and accompany fat deposition Diminished activity is another factor There is good evidence to support the view that carbohydrate is convertible into fat and that glycogen is initially deposited before the extra fat is laid down

Clinical

(1) *Hypothalamus*

Encephalitis meningo encephalitis cranio pharyngiomas (including Fröhlich s syndrome) third ventricle tumours and cerebral injuries may all produce adiposity by involvement of the hypothalamus It is not generally recognized that the virus fevers of childhood and adult life e g measles and mumps are not infrequently complicated by encephalitis and may be followed by adiposity

Apart from the above important considerations it would be contrary to all clinical experience to suggest that hypo thalamic lesions account for more than a minority of cases of adiposity

(2) *Pituitary*

(*a*) *Cushing's syndrome* Although the aetiology of this condition in any one case may be uncertain yet there is no

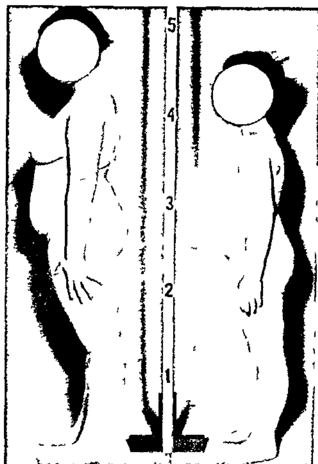


Fig 33 Familial Adiposity The girl aged 14 began to menstruate when 11 menorrhagia note large breasts red lineae distensae kyphosis diffuse thyroid enlargement cyanotic mottling legs also broad pelvis The brother aged 10 shows adiposity with normal sexual development another brother aged 11 is thin

doubt that in some patients a destructive attack on the pituitary gland by deep radiation or by the insertion of radon seeds will ameliorate or cure the condition and cause a loss of abnormal fat deposition It seems sound to conclude therefore that in

such patients the adiposity was due directly or indirectly to over activity of the pituitary gland

(*b*) *Giantism* Tall people may be thin or fat and acromegalics do not tend to be fat Nevertheless adiposity is frequently present in tall people with mild acromegaloid features or in families where tallness is met with among the majority of the members of that family The fatness may be present throughout life or be especially noticeable in the third and fourth decades This rough clinical impression is certainly not beyond criticism but I believe it to have validity and to be comparable to the fat rats obtained by Evans with his original crude pituitary growth extracts It does not imply that the growth hormone of the pituitary gland cannot be secreted in excess with resulting giantism or acromegaly in the absence of adiposity Rather does it suggest that hypersecretion of the pituitary growth hormone may be accompanied by other hyper activity of the anterior pituitary gland leading to adiposity In contrast infantilism of the Levi Loraine type is associated with an absence of fat

(*c*) *Puberty adiposity* Some fat people are fat from birth but in others their pre puberty childhood was associated with normal weight or conspicuous leanness In the latter puberty may be characterized by a coincident increase in weight and the deposition of fatty tissue Puberty is a time of increased pituitary activity and I ascribe the definite clinical entity of puberty adiposity directly or indirectly to pituitary hyper activity The adiposity may continue throughout life Not uncommonly however it diminishes in the late teens and then increases after an interval of some years being accentuated by marriage childbirth and the climacteric In rabbits coitus stimulates the pituitary to activity as is indicated in one direction by ovulation There is no evidence that coitus stimulates the pituitary in women but in patients so predisposed the initiation of a sexual life seems to be associated with a tendency to adiposity

(*d*) *The climacteric* Both in the male and the female the fourth and fifth decades are not infrequently associated with an increase or an initiation of adiposity At this phase there is hyperactivity of the pituitary as shown by the increase of gonadotrophins in the urine I have observed patients ovariectomized

moderate increases in weight are fairly general Some women however put on 20 or 30 lb or more with each pregnancy

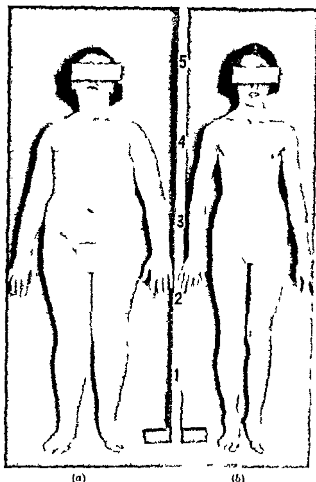


FIG 35 CHILDHOOD ADIPOSITY with some features of Cushing's syndrome (a) Patient aged 14 When 6 years old the patient began to get fat and at 14 she weighed 12 stone Menstruation at 13 Note the broad pelvis plethoric face and mottling and ecchymoses on the legs Headaches troublesome but pituitary fossa normal (b) Control

They may have previously shown a tendency to adiposity but others may have been quite thin In one patient under my care she was so thin before pregnancy that she had consulted several physicians, without success in an endeavour to put on weight

After two pregnancies she consulted me because of adiposity She was rather tall and big boned but otherwise showed no endocrine stigmata Her husband was a scientist and in this case there seemed little or no doubt that appetite and food intake had not increased

In pregnancy there is hypertrophy and hyperfunction of the anterior pituitary gland and of the adrenal cortex

(*f*) *Menstruation* It is very common for adipose patients to complain of a further increase in weight the week before menstruation and its amelioration after There is a good deal of evidence to suggest that this is due to an increased water and salt retention probably because of an over activity of the posterior pituitary gland prior to menstruation (Young has recently demonstrated that water retention is al o produced by anterior pituitary extracts)

(*g*) *Simmonds s disease* This condition (which see) due to destruction of the anterior pituitary gland is generally associated with loss of weight and sometimes with emaciation It is there fore not unreasonable to postulate that the opposite condition of hyperactivity of the anterior pituitary gland is responsible for adiposity in some patients

(3) *Adrenal cortex*

Cushing s syndrome is sometimes due to a tumour of the adrenal cortex which is active and hypersecretory as judged by clinical manifestations androgen assays and the atrophy of the opposite adrenal gland In such cases the removal of the tumour cures the condition and abolishes the adiposity feature of the syndrome One must conclude therefore that in such instances the adiposity was due to hyperactivity of the adrenal cortex

Similar considerations apply to the adrenogenital syndrome when due to an adrenal cortex tumour However we are now faced with a complication of our theories and a paradox Not all patients with this disorder are fat Some even lose the normal amount of fat deposition they had before the onset of the di order especially that which might be termed feminine fat in the breast thigh and buttock areas They accordingly tend to lose their feminine outline and at the same time become muscular The removal of an adrenal tumour will restore their feminine fat In men however an adrenal cortex tumour

produces a deposition of feminine fat and removal of such a tumour causes the loss of this abnormal fat Sexual precocity due to an adrenal cortex tumour is associated with adiposity

In Addison s disease with destruction of the adrenal cortex there is a tendency to lose weight and fat

(4) *The gonads*

Contrary to general belief we have seen in the section on this subject that castration pre or post puberty and eunuchoidism is more often than not associated with thinness rather than fatness although the latter does occur in some case and may even be extreme Further testosterone and probably pro gesterone produce not only an increase in weight and nitrogen retention but also an increase in fat deposition

The influence of castration on fat deposition probably depends upon the degree of reaction of the pituitary and adrenal glands and this depends upon genetic factors

(5) *Pancreas*

The development of islet cell tumours and chronic hypo glycaemia is often but not invariably associated with the onset of adiposity which latter disappears after successful removal of the tumour Insulin given to young diabetics not infrequently produces a degree of adiposity comparable in extent and character to other adiposity-endocrinopathies of childhood Incompletely treated diabetes in children may be associated with fatty enlargement of the liver

Untreated diabetics may be thin or fat Among children and adolescents diabetics are usually thin Among the middle aged diabetics are more usually fat Inadequate treatment of a fat diabetic eventually leads to ketosis and loss of weight However some fat diabetics are as intractable to the treatment of their adiposity by any means as are some non diabetic adipose patients It is tempting to suggest that in these patients the adiposity and the diabetes are both due to pituitary over activity although ultimately the pituitary diabetes leads to degeneration of the islets and a pancreatic diabetes

Lawrence (1941) has recently described a most interesting case of diabetes and lipodystrophy in a woman of 30 associated with lipaemia and hypercholesterolaemia The excess of fat in

the blood disappeared when the diabetes was controlled (some 2 000 units of insulin a day were required) and reappeared when hyperglycaemia was allowed to develop Lawrence postulated that in this case there was an inability to store fat in the tissues and that normally hyperglycaemia leads to hyperlipaemia and fat deposition but in this case the inability to store fat dramatically revealed the process and the tendency to hyperlipaemia He produces other clinical and experimental evidence in favour of the view that carbohydrates are converted to fat and that this is an important action of insulin

(6) *Genetic*

No clinician is in doubt about the genetic determination of adiposity regardless of what the mechanism may be A dramatic illustration of this is seen in Fig 36

(7) *Thyroid*

Myxoedema is by no means necessarily associated with adiposity although thyrotoxicosis usually results in loss of weight including loss of protein and of fat

(8) *Idiopathic*

The majority of cases of adiposity may rightly be labelled idiopathic or unexplained humiliating as this may be for the doctor and tantalizing for the patient However a closer attention to the family background to the clinical history and to the physical examination will reveal in most cases certain endocrine stigmata which are met with in more obvious endocrinopathies

Thus we have the soft feminine baby face sometimes pallid and sometimes plethoric bluish red mottling on the upper arms and thighs on the breasts and on the buttocks and in some cases cutis marmorata of the legs relatively graceful extremities with slender fingers and a curved little finger a broad pelvis in both sexes early sexual maturity in some fat girls and early union of the epiphyses emotional but also social with alternating phases of happiness and depression artistic temperament and in males certain feminine gestures such as putting the hand on the hip and a deficiency of athletic prowess somnolence or relative inertia in some cases an absence of hair on the face or body and in others hirsuties of male type lineae



Fig 36 Familial Pituitary Adiposity To show the incidence of genetic pituitary adiposity affecting three members of a family of six children the other children being normal Ages from left to right are 10¾ years ¾ years 11 months 8¾ years 3¾ years and 1½ years (By courtesy of Dr Dudley Boswell Lowestoft)

distensae on abdomen breasts and axillae white or dusky red some may have a low blood pressure e g 90 systolic 60 diastolic endocrine stigmata or complete endocrinopathies in other members of the family

It seems to me unsound to consider these as due to familial hypothalamic lesions of which there is no evidence My own classification based on the above experimental and clinical considerations is pituitary or pituitary adrenal adiposity the word adrenal being added when hirsutism is a feature If the face is very congested the lineae distensae a dusky red and the legs show skin changes similar to cutis marmorata I hazard the diagnosis of incomplete Cushing s syndrome remembering also that in the child or adolescent this disorder may be associated with premature menstruation and not with amenorrhoea

The fact that only a small proportion of adiposity cases is associated with a full blown typical endocrine syndrome or disease and that so many are very mild and incomplete endocrinopathies apart from the adiposity is quite in keeping with general experience of endocrinology For every classical endocrine disease one meets with there are very many minor and incomplete examples of the same fundamental endocrinopathy

I have no sympathy with the diagnosis of gluttony or alimentary adiposity unless the physician realizes its limitations We know that excessive appetite can be produced in animals experimentally by a hypothalamic lesion or by injections of hormones e g pituitary growth hormone insulin &c It seems probable to me that in so called idiopathic adiposity associated with excessive appetite the latter may be also pathologically determined If for example the pituitary is secreting in excess a hormone which converts glucose into fat the patient will be hungry more will be eaten more fat will be deposited and the vicious circle goes on Starvation diet will nevertheless tend to reduce weight as it does in the more obvious endocrinopathies The response of adiposity to diet is certainly no proof that excessive intake is its fundamental cause

Character and distribution of fatty deposits

Conn (1944) points out as have previous observers that the distribution of fat deposition varies with different endocrinopathies Yet apart from the description of a striking case of



FIG 38 FAMILIAL PITUITARY ADIPOSITY To show the incidence of genetic pituitary adiposity affecting three members of a family of six children, the other children being normal Ages from left to right are 10½ years 5½ years 11 months 6½ years 3½ years and 12 years (By courtesy of Dr Dudley Boswell Lowestoft)

known physico chemical laws if the calorific value of the food intake is less than the calories expended in activity (automatic or voluntary) a person should lose weight or fail to gain it The apparent contradiction of this basic law has led to repeated investigations Newburgh (1944) summarizes these and records his own investigations He finds no essential differences in basal metabolism specific dynamic action of food intake food absorption &c in the normal and the obese, and concludes that adiposity must be explained by an excessive food intake or a decreased energy output He also points out that the basal metabolism may be above normal in fat people and that they may require more food than others to maintain their weight

There is little doubt that pathological hunger either general or for sweet things is an entity and explains some cases of adiposity It is also true that many adipose patients conserve their energy This is noticeable in the consulting room when they may take twice as long as an average patient to dress and undress or in the home when they are not the first to run upstairs to fetch something These features may be a result rather than a cause of the adiposity Nevertheless, from observations in hospitals and nursing homes I cannot rid myself of the conviction that there is another factor in the mechanism and that when patients complain bitterly that they eat less than their associates and still put on weight or fail to lose it we are not dealing with mendacity Goldzieher (1945) a scientific physician courageously records his personal experience on a 900 calorie diet and challenges the views of Newburgh The water retention factor is now recognized but still does not in my opinion solve the enigma of adiposity Just as lipodystrophy or atrophy was explained by an inability of fat cells to take up fat (or an absence of fat cells) so adiposity has been attributed to a special tendency of fat cells to take up fat and to fix it so that its removal from the cell is difficult Such postulations must be resorted to if the changing distribution of fat as in some cases of Cushing s syndrome is to be explained These theories however do not explain the apparent inapplicability of the laws of conservation of energy It probably is only apparent and not real but more work is needed to clarify this complex subject

Cushing s syndrome in which the fat tended to disappear from all the limbs including the proximal parts but was increased on the trunk face and neck he does not attempt any classification on this basis

From my own observations I find it difficult if not impossible to present a consistent classification of endocrine adiposity according to the site of deposition of fat In general fat tends to be deposited on the face and neck breasts and abdomen The upper arm and thighs are usually involved and the fore arms and legs usually escape and may even be graceful In some cases however the legs also become fat and the shape of the ankles disappear In some cases of Cushing s syndrome as in Conn s case the upper arms and thighs remain or become thin while the deposition of fat in the face and neck is considerable

Some cases of adiposity call to mind examples of lipodystrophy in which the disappearance of fat is limited to the upper half of the body These patients do not complain of a disappearance of fat anywhere but rather that the site of excessive fat deposition is limited to the abdomen buttocks and thighs If they are put on a low calorie diet they lose fat from the face and neck where it was not abnormally present and become haggard looking while at the same time they fail to lose fat appreciably from the lower half of the body

Adiposis dolorosa is the name given to a type of adiposity in which the fat areas are painful and in which moods of depression prevail The fat is also distributed symmetrically especially in the thighs and back of the knee joint sometimes in lumps I am unable to take the view that this is a separate pathological or endocrinological entity The name does remind us however that fat depositions may be painful and that depression may be a feature of many forms of adiposity

In considering fat deposition it is important not to concentrate solely on subcutaneous fat Fat is also deposited in the internal organs particularly in the heart muscle and pericardium This is very important for sudden cardiac failure in the third or fourth decade may occur in severe adiposity

The physico chemical enigma in adiposity

Whatever the pathological lesion causing the adiposity or even in the absence of a pathological lesion according to all

dotrophic hormone testosterone oestradiol and other hormones are not usually effective

A diet of 800 calories is given below For further particulars see Simmonds s book on diets

Suggested Diet for Obesity Patients (800 calories approximately)

Breakfast

Tea milk (2 tablespoons)
Two unsweetened biscuits or 1½ Ryvita or Vitaweat or ⅔ oz bread (thin slice) or ⅓ oz toast
Butter piece size of walnut (½ oz)

Dinner

Lean meat—a fair portion about 3 oz
A good plateful of green vegetables or salad
1 small apple orange pear or grape fruit
Two unsweetened biscuits or 1½ Ryvita or Vitaweat or ⅔ oz bread (thin slice) or ⅓ oz toast

Tea

Tea milk (2 tablespoons)
Two unsweetened biscuits or 1½ Ryvita or Vitaweat or ⅔ oz bread (thin slice) or ⅓ oz toast
Butter piece size of half a walnut

Supper

3 oz steamed fish or 2 oz lean meat or cheese
Butter piece size of walnut (½ oz)
A good plateful of green vegetables or salad
1 small apple orange pear or grape fruit
Two unsweetened biscuits or 1½ Ryvita or Vitaweat or ⅔ oz bread (thin slice) or ⅓ oz toast

N B Margarine if butter unobtainable
Fruit and eggs are not essential in war time
Avoid sugar sweets cakes pastries puddings jam bread (except as above) potatoes or fried food
Plenty of green vegetables salad and all fresh fruit except bananas may be eaten when obtainable

Free extras

Vegetables &c The following vegetables &c may be taken in good helpings as free extras they contain only very small quantities of carbohydrates

Asparagus green artichokes French beans cabbage cauliflower celery cranberries cress black currants egg plant stewing goose berries greens horseradish lemons lettuce marrow mushrooms radishes rhubarb salsify scarlet runners seakale spinach tomatoes

Treatment

Where adiposity is part of a major endocrine syndrome the appropriate treatment of the latter is fundamental e g removal of an adrenal tumour Where the condition is less definite it must be appreciated by doctor and patient that there is no hormone available that can cause fat to catabolize or disappear In fact if the majority of cases are due to excessive activity of an endocrine gland one would not anticipate that such a hormone would be available The discovery of a fat catabolic hormone is nevertheless hoped for

For most fat patients therefore one can only hold out the possibility of an amelioration of the degree of adiposity and even this involves a diet well below average in its calorie content Further adiposity will return if the diet is not maintained at a lower level than normal The potency of diet and the ineffectiveness of hormone therapy has been claimed as proof of the glutton theory of adiposity but this is a fallacy since diet is also effective in adiposity due to a pituitary parapituitary or adrenal lesion

When an adipose patient is placed on a restricted diet weight is lost fairly easily during the first 2 weeks and then perhaps becomes stationary This is due to water retention, and if diuretics are given a profuse diuresis often follows I give ammonium chloride in capsules 2×1 gm three times a day after meals followed by an organic mercury suppository or injection e g Neptal Mersalyl Salyrgan 1 c c each evening Urea and theobromine &c are alternative diuretics Some patients have a water retention factor from the beginning so that the diuretic procedure might be given twice or thrice weekly from the start

Thyroid is useful in patients with a slow pulse and may be tolerated in large doses e g 3 grains of thyroideum siccum daily Patients with rapid pulses do not tolerate thyroid well It should be remembered that the basal metabolism is rarely sub normal in adiposity and that the heart may be infiltrated with fat and incapable of beating rapidly without decompensation resulting Anterior pituitary is sometimes given by mouth but there is no evidence in favour of it being effective nor any clear theoretical consideration that justifies its use Gona

CHAPTER XII

LIPODYSTROPHY

CONSIDERABLE attention is given to the excessive deposition of fat but comparatively little to an inability to store fat or its excessive catabolism It is of course well recognized that in severe cases of thyrotoxicosis Addison's disease Simmonds's disease diabetes mellitus diabetes insipidus &c there may be a complete loss of fat from the viscera and subcutaneous tissues There are however a much larger number of people without any obvious lesion who eat well and remain painfully thin In some cases they are obviously the hyperactive and worrying kind but in others the cause is obscure The effect of sub nutrition in causing loss of fat has been seen in anorexia nervosa and in concentration camps

Lipodystrophy is an interesting condition superimposed on apparent normality in which subcutaneous fat is usually lost completely from the face neck upper limbs and upper part of the trunk and is deposited in the lower abdomen buttocks and thighs (The reverse distribution has been recorded by Bigler, 1939) In such cases forced feeding fails to affect the thin parts and increases the adipose parts It has been noted that minor manifestations of this disorder are not as infrequent as is generally supposed and such patients complain of fatness in their abdomen buttocks and thighs

Wells (1940) regards fatty tissue as part of the reticulo endothelial system and as having a functional activity He points out that in lipodystrophy there is not only loss of fat but of the embryonic adipose tissue cells which are capable of storing fat The few autopsies on cases of lipodystrophy have failed to show any endocrine changes but Zondek (1944) refers to one report (Szarbo) where lesions in the corpus striatum were noted Lawrence (1946) recently described a remarkable case of progressive lipo atrophy in a woman of 26 commencing with mild diabetes and a xanthomatous rash and developing into obvious and progressive diffuse lipo atrophy with lipaemia gross enlargement of the liver and spleen and diabetes requiring 2 000 units of insulin a day but showing

Beverages &c

Tea and coffee any milk added is calculated as in Diet Sheet

Bovril Oxo these have no real fattening properties but their salt content may stimulate appetite and cause thirst

Clear soup with green vegetables

Soda water

Saccharine tablets or dust should be used if sweetening is desired Never sugar unless specially ordered (One lump of sugar or one level teaspoonful = 10 gm carbohyrate = 40 calories)

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CHAPTER XIII

DIABETES INSIPIDUS

Definition and Mechanism

DIABETES insipidus is a disturbance of water balance characterized by primary polyuria and secondary polydipsia and due to a destructive lesion of the posterior lobe of the pituitary gland or the adjacent part of the hypothalamus The latter e g an experimental puncture lesion of the tuber cinereum or nucleus supra opticus is followed by atrophy of the posterior pituitary lobe

Cushing (1933) stated that Its secretory product (pars nervosa) is unmistakably derived from the investing pars intermedia whose cells become basophilic when ripened and under nervous impulses from hypothalamic nuclei the basophil cells invade the pars nervosa and become transformed into hyaline bodies which pass into the infundibular cavity However experimentally it is clear that diabetes insipidus can occur in the presence of a normal pars intermedia and that the anti diuretic hormone can be extracted from pars nervosa (posterior pituitary) but not from pars intermedia either alone or associated with an atrophied pars nervosa (Pickford 1945) Fisher Ingram and Ranson (1938) showed that the essential lesion was anywhere in the supra optic tract and Richter (1935) that the diuresis preceded excessive intake of fluid It also occurs for a while even if fluid is completely withheld Excessive quantities of antidiuretic hormone are found in the urine in normal animals subjected to water deprivation or to emotional stimuli (Verney 1946) so that water diuresis may be fitly and accurately described as a condition of physiological diabetes insipidus and there can be little doubt that the anti diuretic secretion of the neurohypophysis is a hormone in the physiological sense its liberation being continuously governed by the contemporary concentration of chloride and possibly of other osmotically active substances in the arterial plasma Pituitrin (or its pitressin component) not only produces inhibition of water secretion by its influence on the kidneys (Winer 1942) but also a transient increase in urinary chloride excretion which

little or no ketosis The patient died after an operation for ovarian cyst Neither the pancreas nor any of the endocrine glands showed pathological changes at autopsy The liver and spleen showed fibrosis but no foam cells Lawrence cites comparable cases and postulates that the fundamental condition was the lipo atrophy and the hyperglycaemia was the result of the absence of conversion of glucose to fat since the latter could not be stored He believes that a normal function of endogenous insulin is to convert glucose to fat

Local atrophy of fat is observed in some people following insulin injections in others areas of hyperplasia of fatty tissue may be present at the site of injection adjacent to the atrophic areas and even when the latter are not present (Wells 1940)

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(5) Hand Schuller Christian syndrome—this is congenital and familial and is characterized by exophthalmos large liver and spleen yellow tinted skin and irregular patches of infiltration of the skull shown by radiography

Treatment

Pitressin 10 to 20 units in 1 c c aqueous solution injected subcutaneously is effective Its duration of action is only a few hours and more recently 1 c c (5 units) of pitressin tannate in oily solution has proved of greater convenience owing to slower absorption at the site of injection the effect of a single injection lasting for 24 hours A dried powder of posterior pituitary e g piton or disipidin is also effective when used as a nasal snuff The dose is 25 to 50 mg t d s The patient learns well enough to estimate the required dose without weighing Excessive dosage may cause a feeling of faintness intestinal spasm and in one of my patients ureteric spasm and dysuria Pitressin solution by the nasal route as a spray is also used Voluntary or compulsory restriction of fluid is illogical since the primary trouble is excessive excretion not intake In severe cases the patient will drink any fluid obtainable even his own urine and will stop at nothing to get fluid

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is subsequently compensated for Thyroidectomy or removal of the anterior pituitary lobe ameliorates diabetes insipidus (Mahoney and Sheehan 1935 Blotner and Cutler 1941)

Incidence

Diabetes insipidus may be familial and then occurs in young people males more commonly than females It may however, occur at any age

Aetiology

The causes of diabetes insipidus are as follows (1) familial (2) tumours in or adjacent to the pituitary (3) inflammatory lesions in the parapituitary region e g encephalitis lethargica basal meningitis syphilis (4) fractured skull (5) xanthomatosis (Hand Schuller Christian s disease)

Clinical Picture

The essential feature is the passage of large quantities (e g 10 litres a day) of pale urine of low specific gravity (usually less than 1010) and good experimental evidence indicates that this is the primary disorder the resulting unquenchable thirst being a secondary phenomenon The tissues become dehydrated there is no obvious perspiration, and the skin and mucous membranes are very dry The faeces are hard and desiccated and the patient constipated Nocturia prevents sleep

Course and Progress

Diabetes insipidus usually runs a chronic course lasting for thirty or more years Death however may follow intercurrent infection

Diagnosis

The differential diagnosis is as follows

(1) Diabetes mellitus—glycosuria
(2) Chronic nephritis—*albuminuria renal casts and hypertension*
(3) Neurosis or hysteria—other stigmata
(4) Caffeine idiosyncrasy—this runs in families and polyuria ceases *if water only is drunk*

(5) Hand Schuller Christian syndrome—this is congenital and familial and is characterized by exophthalmos large liver and spleen yellow tinted skin and irregular patches of infiltration of the skull shown by radiography

Treatment

Pitressin 10 to 20 units in 1 c c aqueous solution injected subcutaneously is effective Its duration of action is only a few hours and more recently 1 c c (5 units) of pitressin tannate in oily solution has proved of greater convenience owing to slower absorption at the site of injection the effect of a single injection lasting for 24 hours A dried powder of posterior pituitary e g piton or disipidin is also effective when used as a nasal snuff The dose is 25 to 50 mg t d s The patient learns well enough to estimate the required dose without weighing Excessive dosage may cause a feeling of faintness intestinal spasm and in one of my patients ureteric spasm and dysuria Pitressin solution by the nasal route as a spray is also used Voluntary or compulsory restriction of fluid is illogical, since the primary trouble is excessive excretion not intake In severe cases the patient will drink any fluid obtainable even his own urine and will stop at nothing to get fluid

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CHAPTER XIV

DIABETES TENUIFLUUS

Definition

A CONDITION of hypersecretion of the posterior pituitary antidiuretic hormone and manifested by inadequate excretion of water by the kidneys and a positive water balance if measured by fluid intake and urinary excretion

I have thought the recognition of this condition sufficiently important to warrant a name and after consultation with Professor H E Butler have adopted the title Diabetes Tenuifluus diabetes (syphon urine) and tenuifluus (flowing slenderly) The opposite condition of diabetes insipidus (tasteless) might better be termed diabetes multifluus (flowing profusely)

Clinical

The condition has not yet been recognized as an entity without other endocrine complications although it is not improbable that it exists as such The retention of fluid before menstruation that is so frequently encountered may be one manifestation The retention of fluid manifested by some people with anxiety is another manifestation and there is some experimental evidence to show that anxiety or nervousness produces excessive secretion of pitressin The water retention factor in adiposity idiopathic or obviously endocrinopathic is probably due to the same cause as is also the water retention which develops after 2 weeks on a very restricted diet Again experimentally a low water intake results in over secretion of pitressin

Acromegaly may be associated either with diabetes insipidus or diabetes tenuifluus according to the phase of the disease In a case of acromegaly which I was invited to see by the late Dr Dorothy Hare because of secondary hirsutism I noticed that the woman was perspiring profusely Measuring the fluid intake and urinary output it became obvious that there was a positive fluid balance Was the perspiration secondary to this or primary? With the collaboration of

Professor Ellinger at the Lister Institute an excess of anti diuretic hormone was demonstrated in the cerebrospinal fluid Deep radiation of the pituitary gland resulted in a disappearance of anti diuretic hormone from the spinal fluid a restoration to a normal water balance (intake output) and the cessation of perspiration Compensatory perspiration does not always occur as it does in acromegaly where there is hypertrophy of sweat glands In other cases e g adiposity there will result fluid retention

E I Jones has described a syndrome in a man of 26 which he attributes to hyperactivity of the posterior lobe of the pituitary gland the main features were hypertension hyperchromic anaemia achlorhydria and impaired carbohydrate tolerance melanophore expanding vasopressor and antidiuretic substances were present in the urine Confirmatory evidence is awaited with interest but it would not appear that the condition can be regarded as the uncomplicated opposite of diabetes insipidus

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SECTION TWO

THE ADRENALS

A PHYSIOLOGY

CHAPTER XV

INTRODUCTION

(a) Development

THE adrenal glands consist of two components an outer cortex and an inner medulla the former being derived from the mesoblastic urogenital ridge and the latter from the neural ectoderm in common with the sympathetic neurones In the human foetus the first development of the cortical component is noted in the fourth week as a proliferation of epithelial cells lying between the mesonephros and the root of the mesentery

Differentiation of the chromophil cells of the medulla from sympathoblasts begins in the 18 mm embryo and is complete at birth then masses of sympathochromophil cells penetrate into the cortical epithelial cells In the elasmo branch fishes the cortex (interrenal body) and medulla (para aortic chromaffin bodies) remain quite separate in reptiles they are in more in timate association but it is only in mammals that the cortex completely surrounds the enclosed medulla

The human suprarenal gland at birth is surprisingly large in relation to the bulk of the kidney This abnormal size is due to a peculiar hypertrophy of the cortex The main mass of the foetal cortex can be differentiated histologically from a narrow outer rim in that it does not contain the characteristic doubly refracting fatty substance of the latter and of the adult cortex (Elliott and Armour 1911) The inner mass of hypertrophied cells degenerates undergoing fatty changes and at the end of the first year all trace of it has disappeared Haemorrhages occur readily in this degenerating zone and are sometimes wrongly interpreted as pathological and not physiological The narrow outer rim becomes the adult cortex

The chromaffin cells of the medulla are identical with masses of chromaffin cells scattered along the ventral surface of the

abdominal aorta in relationship to the sympathetic ganglia These chromaffin paraganglia are relatively hypertrophied in foetal life and tend to atrophy at birth

The development of the suprarenals is partly dependent on the proper development of the cerebral hemispheres and mid brain, as is indicated by the minute size of the adrenals in an anencephalic foetus It would appear however that it is only the inner foetal cortical mass which fails to develop the medulla and outer cortical rim being present (Elliott and Armour)

The adrenals in man lie in contact and immediately above each kidney The right is somewhat triangular in shape like a 'cocked hat but the left is flatter and more crescentic The chief suprarenal vein emerges from the hilum situated on the internal and ventral surface and the right gland is especially closely applied to the inferior vena cava The glands are enclosed in a tense connective tissue capsule

The average dimensions of each gland are 27 mm vertical diameter 47 mm transverse diameter and 9 mm thickness together they usually weigh from 8 to 10 gm but limits of normality are 5 to 15 gm The medulla makes up about 10 per cent of the weight of the gland

Externally the glands appear a brownish yellow colour On cross section the inner medulla appears greyish white or silvery grey or dark brown if the gland is haemorrhagic or congested It is surrounded by a dirty yellowish grey or orange coloured cortex the pigmented zone being represented in the adult as a narrow dark brown zone or line on the inner rim of the cortex and separating it from the white medulla

(b) Blood supply

The adrenal is a highly vascular organ receiving its main blood supply from the suprarenal artery and branches from the renal artery The right suprarenal vein drains directly into the inferior vena cava but the left goes to the renal vein There are also venous anastomoses in the adrenal capsule with connexions to the perirenal venous plexus The longitudinal musculature of the adrenal veins is particularly well developed

The nerve supply is chiefly from the coeliac plexus but branches are also received direct from the splanchnic nerves and phrenic and renal plexuses all the fibres interlacing to form the

suprarenal plexus The neural impulse is transmitted some what paradoxically by liberation of acetyl choline at the terminal ganglia

(c) Histology

The cortex of the suprarenal is composed of polygonal epithelial cells arranged mainly in columns (zona fasciculata) with an inner network of trabeculae adjoining the medulla (zona reticularis) and a narrow outer zone beneath the capsule (zona glomerulosa) The cells in the latter zone tend to be small and round with deeply staining nuclei and vacuolated protoplasm The cells of the adrenal cortex are rich in lipoid which is especially concentrated in the zona fasciculata as is well shown by fresh sections stained for fat The zona reticularis is highly vascular and the cells tend to be large rounded and well defined often isolated by capillary spaces They contain special pigment granules closely packed in the cell protoplasm frequently obscuring the nucleus They appear as golden to green if sec tions are stained with methylene blue and eosin The granules are said to appear at puberty and to increase with advancing age

The cells of the medulla are polygonal and columnar arranged in irregular anastomosing columns surrounding or permeated by sinus like blood vessels The arrangement leaves little doubt that the materials they secrete find their way directly into the blood spaces and in fact the blood in the sinuses may give the green reaction with ferric chloride which is characteristic of adrenaline The cell protoplasm contains chromophil granules which stain brown with chromic acid

(d) Adrenalectomy

Unilateral adrenalectomy in the normal animal has no detect able effects and our consideration is therefore limited to com plete bilateral adrenalectomy in the absence of accessory adrenal glands It is necessary to experiment on different species of animals to be able to study all aspects of adrenal function Since death usually follows within a week of operation a study of more chronic deficiency is only made possible by the giving of made quate doses of cortin Sometimes however untreated adrena lectomized animals may live for weeks or months owing to the

existence of accessory adrenal glands which however are not sufficiently potent to prevent some degree of adrenal inefficiency

Since adrenaline injections have no appreciable effect on the course of events after adrenalectomy and since a cortical extract free from adrenaline can maintain life and restore normal functions it can be concluded that the effects of adrenalectomy are due to absence of the essential hormone or hormones of the adrenal cortex The more detailed effects of the operation are best considered in conjunction with the results of injecting cortical hormones In general however adrenalectomized animals are weak and apathetic with poor muscle tone deficient appetite inability to gain or maintain weight inability to withstand cold susceptibility to infection or traumatic shock and a tendency to enter suddenly a phase of crisis resulting in rapid death In some species the animals may appear normal to superficial observation for some days and sudden death may surprise the uninitiated observer

Autopsy of the adrenalectomized animal reveals among other changes considered later a diffuse lymphoid hyperplasia and enlargement of the thymus gland Although terminal pulmonary infection is not infrequent it is not constant and the specific cause of death is not revealed by morbid anatomy alone

It is important to realize that the adrenal cortex in addition to its potentialities for producing widespread and dramatic pathological effects is a vitally important gland in human physiology and has a continuous dynamic function Thus Vogt (1943) showed collecting blood from the suprarenal vein of a dog that the life saving cortical hormones were continuously secreted and that the potency of 1 c c of plasma obtained from this source was ten times as great as the activity contained in the extract from 1 gm of gland The rate of secretion under the conditions of the experiment indicated that a 10 kg dog secretes from both adrenal glands the equivalent of 230 c c of a commercial extract per 24 hours This however is some twenty times the daily amount apparently required to keep an adrenalectomized dog alive although not necessarily completely normal

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ESSENTIAL HORMONES OF THE ADRENAL CORTEX

(a) Introduction

Initial work on the hormone treatment of adrenalectomized animals was carried out with an extract of the adrenal cortex prepared by Swingle and Pfiffner in 1929 (other extracts of proved potency were those of Hartman Stewart and Rogoff) This and similar extracts were subsequently shown to contain several hormones and more exact study was made possible by the isolation of a series of hormones (two or more of which may be considered essential in the treatment of adrenal insufficiency) by Reichstein and colleagues (1936–7) in Europe and by Kendall Mason and colleagues (1938 and 1942) at the Mayo Clinic in America Another series of hormones concerned with sex function but not essential for the successful treatment of adrenalectomized animals have also been isolated by the same group of workers the initial step having been taken by Reichstein in the isolation of adrenosterone However all the hormones of the adrenal cortex are steroids which although having very different physiological actions are very closely related chemically the progesterone formula constituting the basic structure To some extent they are interchangeable by manipulations of the biochemist *in vitro* and probably similar chemical or metabolic processes occur in life This interchangeability extends even to hormones of apparently completely different functions Thus Kendall s Compound E 11 dehydro 17 hydroxycorticosterone the action of which is mainly on carbohydrate metabolism and which is also partially effective as substitution therapy for adrenalectomized animals can be oxidized to a diketone which is devoid of these functions but which can stimulate comb growth in the capon and is therefore an androgenic hormone The essential hormones of the adrenal cortex will be studied under four headings according to their functions

(1) Water and sodium metabolism—desoxycortone
(2) Carbohydrate metabolism—the corticosterone group of which the three most studied are corticosterone 11 dehydrocorticosterone and 11 dehydro 17 hydroxycorticosterone (Kendall s Compound F)
(3) Amorphous fraction (Wells and Kendall)—life saving and renal function

(4) Sex hormones—adrenosterone (androgenic) oestrone and progesterone

(b) Desoxycorticosterone (Desoxycortone) and the Metabolism of Sodium, Chloride, Potassium, and Water

Marine and Baumann in 1927 observed that in adrenalectomized cats the blood sodium was decreased and the blood potassium increased This was a fundamental observation which was apparently lost sight of and for the next 5 years in spite of a plethora of work both experimental and clinical on the adrenal glands no one appears to have realized or at least to have stressed their important influence on sodium and potassium As in many scientific advances attention was focused on this essential function of an endocrine gland by the imaginative investigation and elaboration of a clinical observation Thus in 1932 Loeb noticed that a patient with Addison s disease showing signs of severe adrenal insufficiency bore a close resemblance to patients suffering from medical or surgical shock Since it has long been known that in the latter condition salt is lost from the body Loeb investigated this possibility in Addison s disease He found that there was an increased excretion of sodium and chlorine low serum values for these elements and a retention of potassium with high serum values Further the condition of the patient could be aggravated by withdrawing salt from the diet and ameliorated by giving salt Later (1935) with Atchley and Stahl Loeb showed that similar phenomena could be observed in the adrenalectomized dog and could be controlled by cortin or salt He suggested that the most attractive hypothesis which may be advanced at this time is that the adrenal cortex serves as a regulator of sodium metabolism The brilliant work of Loeb and his collaborators has been repeatedly confirmed by many experimentalists and clinicians and it is now established that the influence of the adrenal cortex on sodium (as well as chlorine and potassium) is as specific as that of the parathyroid glands on calcium and phosphorus

The mechanism of this function and its correlation with water balance needs more careful consideration The metabolism of sodium is closely tied up with the metabolism of water About 60 per cent of the body is water and some two thirds of the

body water is in the body cells The remaining one third is in the plasma lymph cerebrospinal fluid, and intercellular spaces the whole of these being conveniently termed the extracellular fluids The osmotic pressure of the cellular fluids tends to be equal to that of the extracellular fluids The bulk of the cellular osmotic pressure is due to potassium salts and that of the extracellular fluids to sodium salts the cellular membranes are freely permeable to water but not to sodium or potassium or other metallic radicals McCance (1936) pointed out that if sodium is excreted in excess by the body no matter what the cause the organism reacts in two ways (*a*) it excretes more water with the sodium in an attempt to maintain the osmotic pressure of the extracellular fluids with however a corresponding loss of volume of intracellular fluids (*b*) partially failing in this attempt the osmotic pressure of the intracellular fluids decreases and a corresponding fall in the osmotic pressure of the cells results by a transference of water to the cells There results a severe reduction in the volume of extracellular fluids with signs of anhydraemia viz a rise in the percentage of haemoglobin and plasma proteins This is the picture that occurs after adrenalectomy and in Addison s disease Britton and Silvette (1934) demonstrated that in fact the liver and skeletal muscle of the adrenalectomized cat become hydrated while the blood becomes viscous and dehydrated and the blood volume severely decreases The adrenalectomized animal has an increased excretion of water for some days after operation with a negative water balance later there is a decreased excretion but still a negative water balance as the intake of fluid becomes less preceding death there may be suppression of urine Swingle Pfiffner Voss and Parkins (1934) showed that the negative water balance was inadequate to account for the degree of dehydration and haemoconcentration the other factor as explained above being a transfer of fluid to the tissue cells of the liver and muscles

Adrenalectomized animals may be kept in reasonably good condition and their life prolonged by the administration of salt in large quantities without any cortin but most observers find that life cannot be prolonged indefinitely If however sodium bicarbonate is given as well as sodium chloride adrenalectomized dogs are apparently maintained in good health indefinitely

(Harrop 1935 and Allen 1935) This may be due to the fact that the sodium bicarbonate compensates for the decrease in alkali reserve in the adrenalectomized animal Even so however according to Allen (1935) such animals are very sensitive to slight change and life is precarious Since sodium chloride may be replaced by other sodium salts e g phosphate bicarbonate citrate without any obvious deleterious effects it would appear that the sodium is the essential element or at least more important than the chlorine The retention of potassium and rise in its serum value is considered to be a secondary effect of the disturbance of sodium metabolism since the giving of sodium chloride in adrenal insufficiency results in a return of potassium metabolism to normal it is also true however that the feeding of potassium causes an increased excretion of sodium and chlorine and precipitates a crisis These changes in mineral *and water metabolism are prevented or corrected by desoxycortone* or by cortical extract They are not appreciably influenced by corticosterone Adrenalectomized animals treated by injections of desoxycortone may survive indefinitely but they are not normal In particular are they sensitive to cold and infections and may become hypoglycaemic These disturbances of function are corrected by another essential hormone corticosterone Both desoxycortone and corticosterone are ineffective by mouth and must be injected

(c) Corticosterones and Carbohydrate Metabolism

All the members of the corticosterone series are oxygenated at C_{11} being characterized by the presence of an hydroxyl or carbonyl group in this position and it is this chemical feature which apparently determines their potent effect on carbohydrate metabolism The three members of this group whose physiological properties have been chiefly studied are corticosterone 11 dehydrocorticosterone and 11 dehydro 17 hydroxycorticosterone The latter substance is also called Compound E (Kendall) and unlike corticosterone it has some life maintaining properties in addition to its influence on carbohydrate metabolism Nevertheless the essential feature of all members of the group is the action on carbohydrate metabolism and it is probably this action which also determines the resistance to stress toxic substances and shock The corticosterones unlike

desoxycortone when given to normal animals produce atrophy of the adrenal cortex

The growth of our knowledge of the influence of the adrenal glands on carbohydrate metabolism is not without interest Thus Wyman and Walker (1929) suggested as a result of experiments on the adrenalectomized rat that the cortex is concerned in the steady maintenance of a normal blood sugar level while the medulla is an important adjunct for rapid adjustment under emergency conditions There is a good deal of evidence to support this view and in some respects the effect of the two components of the adrenal gland on carbohydrate metabolism is comparable to that of anterior and posterior lobes of the pituitary gland The blood sugar of normal rats is on the average 80 mg per 100 c c and after adrenalectomy it tends to fall to 60 mg with the onset of symptoms of insufficiency and to 30 mg in the terminal stage In more chronic insufficiency the blood sugar may be normal or slightly subnormal but the withdrawal of food or exposure to cold will produce fatal hypoglycaemia

Britton and Silvette (1932) were the first to suggest that the regulation of carbohydrate metabolism may be considered as a prepotent function of the adrenal glands Although this is generally considered an extreme view they have shown conclusively that it is a vital part of adrenal cortex function and *that glycogenic and glycemic changes do not occur after adrenal* medulla extirpation but adrenalectomy may be restored to normality by injections of cortical extract After adrenalectomy in rats they found that the blood glucose and liver glycogen showed marked reduction from normal levels there were also associated decreases in muscle glycogen and increases in blood lactates but the glycogen of heart muscle was not reduced In adrenalectomized guinea pigs cats and marmots the liver glycogen was practically depleted and the blood glucose critically reduced (1934) Completely adrenalectomized animals show a markedly reduced ability to store liver glycogen after glucose injections normal animals storing ten times as much

The normal cycle in carbohydrate metabolism liver is glycogen → blood sugar → *muscle glycogen* → *blood lactic acid* and → liver glycogen Since the blood lactic rises after adrenalectomy, and since the livers of adrenalectomized animals are unable

to remove lactic acid from the blood at a normal rate (Buell and others 1936) it would appear that the adrenal cortex is essential for the change of lactic acid into glycogen especially as there is no evidence that insulin or adrenaline directly influences this link in the chain (Simpson 1936)

Long Katzin and Fry (1940) studied the influence of adrenalectomy on rats and mice maintained on salt When fed there was no obvious effect on carbohydrate metabolism but when starved the liver glycogen decreased and subsequently also the muscle glycogen there was a fall in blood sugar with hypoglycaemic convulsions in the terminal stages Cortical extract or corticosterone restored the blood sugar and the hepatic glycogen to normal but muscle glycogen was not apparently affected

A more complete understanding of the action of corticosterone on carbohydrate metabolism is afforded by wider experimental studies Thus corticosterones produce a great increase in the severity of the diabetes of partially depancreatized rats and an increase in the excretion of nitrogen indicating that the increased excretion of sugar was associated with a breakdown of protein This diabetogenic effect was also demonstrated by producing an increase in severity of phloridzin diabetes and the source of the extra glucose being protein was proved by the ratio of glucose to nitrogen remaining 3 6 to 1 0 In addition to this gluconeogenesis however there is an inhibitory effect of corticosterone on the oxidation of glucose Studies of the respiratory quotient show that the oxidation of glucose is accelerated in adrenalectomized animals and that corticosterones correct this In normal or adrenalectomized animals corticosterones will prevent or counteract hypoglycaemia produced by insulin In addition to gluconeogenesis and the inhibition of excessively rapid oxidation of glucose corticosterone has another action namely the formation or maintenance of hepatic glycogen This is apparently affected by inhibiting the breakdown of hepatic glycogen and by facilitating its formation from glucose or the intermediate substance lactic acid In normal animals as well as in adrenalectomized animals corticosterones produce an increase in blood sugar and hepatic glycogen but such effects are less easily demonstrated in the normal animal and depend upon the species and size of the animal (More recent

work on the adrenals and carbohydrate metabolism has been carried out by Long and colleagues (1940) and Ingle and colleagues (1941 and 1944))

It has been shown that human urine contains certain substances resembling in chemical characteristics and biological action certain of the 11 oxycorticosteroids Urinary extracts have been measured biologically (deposition of glycogen in the liver of adrenalectomized rats) or colorimetrically the two methods giving comparable results (Scowen and Warren 1946) The urinary output per day in normal men and women is about 0 25 mg whereas in Cushing s disease it may be as high as 12 mg per day As might be expected the 11 oxycorticosteroids or glycogen steroids as they have been termed are not excreted in excess in uncomplicated virilism even when the 17 ketosteroids are considerably raised (Scowen and Warren 1946)

Hartman (1947) recently described a fat factor which he believes he has separated from the glycogen steroids and other adrenal hormones In normal starved animals depot fat is mobilized and deposited in the liver whereas this does not occur in adrenalectomized animals unless Hartman s factor or hormone prepared from the adrenal cortex of cattle is injected

(d) The Amorphous Fraction

It is of considerable theoretical and clinical interest that Wells and Kendall in 1940 prepared a highly concentrated amorphous fraction from extracts of the adrenal cortex which contained only traces of crystalline substances related to corticosterone and desoxycortone and without showing to any extent the specific action of these substances (see above) was nevertheless far more potent weight for weight in maintaining the life of adrenalectomized animals than was any known crystalline fraction It also had the most favourable influence on renal function as judged by the maintenance of the blood urea of adrenalectomized animals at normal levels The disturbance of renal function in adrenal insufficiency may however also be corrected by desoxycortone or even by salt only Banting and Gairns (1926) found epithelial degeneration of the tubules of adrenalectomized rats together with albuminous casts erythrocytes and leucocytes Similar observations were made by Simp

son and Korenchevsky (1934) who also found that such changes could be prevented by small doses of cortical extract Initial observations were however made by Marshall and Davis (1916) who found a rise in blood urea and non protein nitrogen and a deficient excretion of injected phenol sulphonaphthalein in adrenalectomized cats They concluded that there was a marked lowering of kidney efficiency even when the general condition of the animal was still good and the blood pressure normal and they postulated that a substance secreted by the adrenals was necessary for the maintenance of normal renal function

(e) Sex Hormones of the Adrenal Cortex

For many years a relationship between the adrenal cortex and the gonads was suspected because of the association of sexual precocity pseudo hermaphroditism and virilism with adrenal tumours It was also well known to the physiologists that the adrenal cortex underwent hypertrophy during pregnancy (e g guinea pigs) oestrus (e g frogs) ovulation (e g pigeons) and after castration (e g rats) the latter change influencing chiefly the zona fasciculata and reticularis (Hall and Korenchevsky 1938) Bilateral adrenalectomy was followed by severe interference with sexual function Thus Freed Brownfield and Evans (1931) found that the testes became pale soft and oedematous and histologically showed ragged fragmented and disorganised spermatic tubules spermatocytes were severely affected staining ghost like with eosin Martin (1932) obtained suppression or irregular appearance of the oestrus cycle in about 88 per cent of adrenalectomized rats The ovaries were one third to one half of the normal size and contained solid masses of persistent corpora lutea there were a few small follicles but no large mature ones Carr and Connor (1933) found a cessation of oestrus degeneration of corpora lutea abortion and cessation of lactation in the adrenalectomized rats Parkes and Selye (1936) showed degeneration of the testes of incompletely adrenalectomized birds and the appearance of capon plumage Martin (1932) believed that the adrenals influence the sex organs indirectly through the pituitary since (*a*) gonadotrophin from sheep s pituitary restores the oestrus cycle (*b*) the hypophysis of the adrenalectomized rat when transplanted had a subnormal

gonadotrophic power and (c) degenerative changes can be demonstrated in the hypophysis of the adrenalectomized rat

In 1927 Howard drew attention to a transitory zone in the mouse adrenal which shows age and sex relationships This X zone is conspicuous in the female mouse as a zone of small darkly staining lipoid free cells surrounding the medulla disappearing with pregnancy or in later life In the male mouse the X zone disappears at puberty (38 days) reappears after castration and can then be made to disappear again with testosterone injections (Deanesly and Parkes 1937) This zone has not been observed in the dog cat rabbit or cow but it may be comparable to the large inner cortical zone in the human foetus designated by Grollman (1936) as the androgenic zone Goormagtigh (1922) quoted by Grollman believes that this androgenic zone is represented in the adult by the inner pigment of the cortex which he has observed to undergo hyperplasia at the menopause Broster and Vines (1933) have drawn attention to a fuchsinophil reaction in some cells of the foetal adrenal cortex—it can be obtained in the male between 10 to 17 weeks and in the female between 11 and 15 weeks As a similar fuchsinophil reaction occurs in the adrenals in virilism it is suggested that such cells may have a sex function and may be *comparable to X zone and androgenic zone Although these* varying descriptions in man and mice are not conclusively correlated there does appear to be histological evidence of a differentiation of special cells in the adrenal cortex associated with sex development and function

The problem was taken a step farther when it occurred to me in 1932 whilst working at the Lister Institute in Professor Korenchevsky s Department of Experimental Endocrinology to investigate the urine of women suffering from virilism for its content of androgenic hormone The initial results reported to the Royal Society of Medicine in December 1933 showed large quantities of androgenic hormone *five times that found in* normal control women The test animal was a castrated rat and the measurement was biological namely increase in weight of prostate and seminal vesicles when injected with a urinary extract

Womack and Koch (1932) using comb growth of capons as their testing method found that normal men and women both

excreted androgens in the urine in approximately equal amounts Paul de Fremery investigated my first case by the comb growth method obtaining a similar result to the prostate assay and *subsequent in a series of virile women the urine showed* amounts of comb growth hormone in excess of normal To gether with Dr Alison Macbeth we published our results in 1936 in the *Journal of Endocrinology* and although at the request of my collaborators my views on the adrenal origin of these androgens were stated more tentatively than I wished the hypothesis was nevertheless put forward It was subsequently discussed by me on my initiative with Callow and Parkes at the Medical Research Institute and arising out of these conver sations and a consideration of an interesting case of extreme virilism following ovariectomy (Kovacs 1932) Callow and I collected and investigated a number of ovariectomized women the results giving a further indication that androgens were secreted by the adrenal glands The results were presented by Callow to the Royal Society of Medicine in 1938 and Parkes (1945) has recently given a most comprehensive review on this field of research In the year 1938 I also met with a case of feminism in a male from whom an adrenal tumour was then removed by the late Cecil Joll and Burrows of the Cancer Hospital demonstrated an enormous excess of oestrogens in the urine of this patient The work of the 1932–8 period has formed the background of an enormous field of research in many dif ferent centres and as it is an aspect of my experimental and clinical research that has given me sound satisfaction I have ventured to indulge in a short paragraph of personal narrative

The final proof of the secretion of androgens and oestrogens by the adrenal cortex however fell to the lot of the biochemists as it inevitably had to Thus in 1936 Reichstein isolated from the adrenal cortex a crystalline steroid adrenosterone and in 1938 Beall isolated oestrone from adrenal extracts Beall and Reich stein in the same year isolated progesterone from concentrates of ox adrenals and it has since been shown that some virilized women secrete an excess of pregnanediol in the urine It has there fore been fully demonstrated that the adrenal cortex secretes in addition to its life saving hormone a series of sex hormones comparable to if not identical with those secreted by the testis and ovary

gonadotrophic power and (c) degenerative changes can be demonstrated in the hypophysis of the adrenalectomized rat

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Womack and Koch (1932) using comb growth of capons as their testing method found that normal men and women both

(f) Standardization of Adrenal Cortical Hormones

The obvious method for the assay of a hormone essential to life is to ascertain the daily dose required to maintain an adrenalectomized animal in good condition Thus the maintenance dose of a certain cortical extract for some different species was found to be rats ¼ to 1 c c dogs 1 to 2 c c cats 2 to 3 c c, monkeys 6 to 12 c c man 10 to 30 c c The method however is of limited value on account of species differences whether as judged by the dosage required for the whole animal or per kilogram body weight variations of individual animals or of different strains or colonies the difficulty of defining and detecting clinical criteria with scientific accuracy and the variability in potency of different batches of cortical extract

A better approximation to scientific accuracy is suggested by other methods e g (1) measurement of the contractile power of the gastrocnemius muscle of an adrenalectomized rat before and after cortical extract (Everse and de Fremery 1932 Ingle 1940) growth of young rats (Grollman and Firor 1933 Britton and Silvette 1937), resistance to the toxicity of histamine or to infective agents (Perla and Gotterman 1931) inability to maintain temperature on exposure to cold (Wid strom 1935) and the maintenance of a normal blood urea and non protein nitrogen the dog unit being defined as the minimum dose per kilogram of body weight necessary for the maintenance of a dog for a period of 7 to 10 days without loss of body weight and elevation of N P N level of the blood (Harrop Pfiffner Weinstein and Swingle 1933 1934)

These various methods of assay did not give results which were strictly comparable and the isolation of a number of hormones from the adrenal cortex each with different physio logical actions has explained the discrepancies The use of a chemically pure substance e g desoxycorticosterone or 17 hydroxy 11 dehydrocorticosterone obviates the necessity for assay as a complete indication of its potency is given by its weight in milligrams Liquid extracts of the suprarenal cortex prepared by different methods contain different proportions of these two hormones (and of others) and their assay depends upon whether one is testing for the desoxycorticosterone content or the corticosterone content The desoxycorticosterone content

Zuckerman (1940) believes that the adrenal cortex secretes sex hormones with a periodicity comparable to that of the ovary since spayed monkeys injected with a constant dose of oestrone showed a periodic uterine bleeding which was not present in spayed adrenalectomized animals kept alive by desoxycortone

The rhythmicity both of the ovary and the adrenal cortex is probably inherent in the hypothalamic pituitary mechanism which probably controls the secretion of both gonadotrophic and corticotrophic hormones

Progesterone and the adrenals We have already noted that Beall successfully isolated progesterone from the adrenal cortex of oxen but the position of progesterone requires a little further consideration Thus Emery and Greco (1940) found that progesterone was as effective as desoxycorticosterone in prolonging the life of and maintaining growth in adrenalectomized female rats Waterman and collaborators (1939) however recorded that progesterone was completely ineffective in adrenalectomized dogs and I personally have not found it of appreciable use in Addison s disease on its own Nevertheless many observers have recorded that pregnant animals in which the secretion of progesterone is considerably increased withstand bilateral adrenalectomy much better and for longer periods than non pregnant animals Further progesterone administered to normal animals over a period results in atrophy of the adrenal cortex in the same way as does corticosterone and allied compounds It would therefore appear that progesterone may act in the same way as the corticosterones rather than like desoxycorticosterone or it may be converted by the tissues to corticosterone like substances In any case the atrophy of the cortex produced by progesterone may prove of great value in diminishing pathological hyperplasia of the adrenal cortex e g in virilism

It is interesting to note that desoxycortone has a progesterone like action on the uterine endometrium of the monkey (Zuckerman 1940) and causes lobule alveolar growth in the monkey s mammary gland comparable to that caused by progesterone (Speert 1940) It also may produce gynaecomastia in man as I have personally observed in two cases of Addison s disease treated by desoxycortone

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CORTICOTROPHIC HORMONE

Hypophysectomy results in atrophy of the adrenal cortex and extracts of the anterior pituitary gland restore the adrenal cortex to normal Such crude extracts may influence other endocrine glands but physico chemical methods have permitted a separation of the pure corticotrophic hormone which is a relatively small molecule and passes through appropriate collodion membranes (Reiss 1944 Neufeld and Collip 1943

is indicated by (1) survival rate (2) growth curves (3) the maintenance of normal serum sodium chloride, and potassium values and (4) the maintenance of normal blood urea in adrenalectomized animals injected with the cortical extract The corticosterone(s) activity may be tested by (1) inability to withstand cold (2) depletion of hepatic glycogen and development of hypoglycaemia when exposed to cold or stress and (3) poor performance of muscular work (gastrocnemius contraction to electrical stimuli) both as to intensity and duration Since both these groups of function are necessary for a patient suffering from Addison s disease cortical extracts should be assayed for their desoxycorticosterone and their corticosterone(s) activity but in most cases such a practice has not been carried out for the commercial extracts available

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basophils This would suggest that the basophil cells secrete corticotrophic hormone which is in keeping with the association of cortical hyperplasia and a basophil adenoma but it must also be remembered that cortical hyperplasia occurs with an eosinophil adenoma of the pituitary as in acromegaly

The corticotrophic hormone plays an important part in the alarm adaptation reaction described by Selye

Corticotrophic hormone has been standardized in two ways (1) by the increase in weight of the atrophied cortex of hypophysectomized animals and (2) by the disappearance of the sudanophobe zone in the zona fasciculata in hypophysectomized animals and its replacement by lipoid containing cells which take the Sudan stain in the same way as the other zones of the cortex It is obvious from the work of Colla and Reiss (1941) that the first method does not indicate the lipoid restoring function of a corticotrophic substance

At this year s (1947) meeting of the Association for the Study of Internal Secretions in America a series of important papers were read on the corticotrophic hormone (called ACTH) Deane and Bergner showed that in fasting normal rats it produced decrease of the cholesterol content of the adrenal gland increase in the liver glycogen and decrease of the sudanophilia of the zona fasciculata as well as increase in the weight of the adrenal gland and decrease in the weight of the thymus Hills Forsham and Finch found that 25 mg of ACTH injected intramuscularly in man caused within 4 hours an increase in neutrophils and a decrease in eosinophils Mason Power Rynearson Li and Evans found an increase in the urine of glycogen corticosteroids and 17 ketosteroids Thorn Prunty and Forsham found that ACTH in a man with hypopituitarism produced a seven fold increase in the excretion of 11 oxy steroids with increased fasting blood sugar and elevated glucose tolerance curve a five fold increase in the excretion of 17 ketosteroids a retention of nitrogen a retention of sodium an increased polymorphonuclear leukocytes and eosinophils and a striking increase in the excretion of uric acid (102 per cent) These changes are much more marked in hypopituitarism than in normal people and do not occur when the adrenal cortex is destroyed as in Addison s disease All this work is of considerable theoretical and practical clinical importance A further recent study by Sayers

Li Simpson and Evans 1942) The term adrenocorticotrophic hormone has been used for this hormone but it has no effect on the adrenal medulla or on the secretion of adrenaline I have preferred the abbreviation corticotrophic which by common consent can be considered as referring to the cortex of the adrenal gland there being no likely source of terminological confusion in endocrinology

It may be that the corticotrophic hormone of the pituitary gland influences the secretion of all the hormones of the adrenal cortex as is suggested by the power of remnants of adrenal cortex to undergo complete hyperplasia but specific proof of its influence is more easily forthcoming in some directions than in others Thus Gratton and Jensen (1940) showed that pituitary corticotrophic hormone exerted a pronounced anti insulin effect and a deposition of liver glycogen in mice comparable to that of the corticosterones It is equally effective in restoring the bodily resistance of hypophysectomized animals to harmful substances e g morphine and histamine (Perla 1935) The diminution of fat in hypophysectomized animals is restored by corticotrophic hormone (Reiss et al 1937) The secretion of androgenic hormone following corticotrophic hormone is indicated by the increase in size and weight of the prostate and seminal vesicles of castrated rats (Davidson 1937 Davidson and Moon 1936) Corticotrophic hormone is found in pregnant mare s serum but whereas it restores the weight of the atrophied adrenal cortex of the hypophysectomized rat it does not restore the lipoid disposition and normal histology of the gland as does pituitary gland corticotrophic hormone The latter therefore must contain more than one type of corticotrophic hormone as might well be expected

Koneff (1944) has pointed out that corticotrophic hormone has wide effects on the endocrine system of the intact animal producing atrophy of the thymus and lymph nodes retarded development of testes and male accessory organs hypoplasia of the thyroid and retardation of body growth Some of these effects are probably produced by its effect on the pituitary gland in which corticotrophic hormone produces decrease in the size of the basophil cells with loss of their granular material and changes in the cell nucleus changes which Koneff interprets as indicative of retarded or depressed functional activity of the

B CLINICAL

CHAPTER XVI

HYPERCORTICALISM

(a) Introduction

If one considers this complex subject from an historical point of view or even from a purely clinical point of view the reader or observer may find it difficult to develop unequivocal ideas or clear cut classification If one adds to the wealth of clinical material more scientific studies of biochemical biological and histological aspects there does not necessarily follow that intellectual illumination that might be expected and a cynic might speak of confusion worse confounded This however is not really the case although there are still some fundamental links in the chain of evidence to be elucidated Accordingly it is my intention to attempt a rationalization of existing knowledge aiming at lucidity undivorced from factual evidence and indicating discrepancies or obscurities where such exist The basis of this presentation rests upon clinical and pathological observation as well as biological assay

I have proposed the use of the term hypercorticalism instead of the laborious phrase hyperfunction of the adrenal cortex or the misleading word hyperadrenalism which should be limited to hyperfunction of the adrenal medulla The term hypercorticalism may be applied to the hyperfunction of any one of the several aspects of cortical function These may be classified under three main headings (1) sexual—androgenic or oestrogenic (2) diabetic or gluconeogenic and associated metabolic disorders e.g fat and (3) salt water metabolism and those other associated factors which are deranged in a deficiency direction in hypocorticalism (Addison s disease) Not infrequently the first and second functions are excessive while the third is undisturbed and in some circumstances this over activity is associated with an actual deficiency of the third function as if the cells responsible for the first two functions have invaded and destroyed those responsible for the third

Liang and Long (1946) indicated that the presence of large quantities of ascorbic acid in the adrenals is not merely storage since ACTH injected into rats produced a considerable fall in the cholesterol and ascorbic acid content of the rat's adrenal

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(by injection) will produce involution or atrophy of the contralateral gland or of both glands In the case of a single gland such as the thyroid administration of thyroxine will produce atrophy of the thyroid gland

The anomaly of corticotrophic hormone apparently being secreted both by eosinophil cells (acromegaly) and by basophil cells (Cushing s syndrome) has been considered in the physiological section (vide Section 3)

(d) Biological Considerations

The effects of hypercorticalism in the first five conditions namely pseudo hermaphroditism sexual precocity adreno genital syndrome Cushing s syndrome and acromegalic virilism may all be explained by an excessive secretion of androgenic hormones by the adrenal cortex for which there is abundant proof (see Physiology section) (In the case of sexual precocity in girls there may also be an excessive secretion of oestrogenic hormones although the precocity is not usually a true precocity) In the rare cases of feminization of the male there is unequivocal proof (Simpson and Joll 1938 Burrows and colleagues 1936) that a great excess of oestrogenic substances are secreted by the adrenal cortex a moderate excess of oestrogens may also be excreted in the first five conditions (Simpson et al 1936 Frank R T 1937) but not comparable in amount to that in feminization There are as yet no conclusive histological findings to explain these biological differences in behaviour of adrenal cortical tumours or hyperplasias in males and females Ross found discrete fuchsinophil granules in adrenal tumours producing virilism in women but not in an adrenal tumour producing feminism in man Her findings are reported by Simpson and Joll (1938) However her colleague Sudds found such granules in 24 per cent of normal adult male suprarenals and 28 per cent of adult female suprarenals 11 oxycorticosteroids are found in excess in the urine in Cushing s syndrome but not in uncomplicated virilism

(e) Adrenogenital Syndrome

(i) *Definition* This syndrome has been described under a variety of names by many clinicians in different countries over the past 50 years but a comprehensive definition is not easily

function Thus in the adrenogenital syndrome or in Cushing s syndrome there may be evidence in some phases of an incomplete Addison s disease and as far back as 1909 Winkler (quoted by McGavack 1940) recorded two cases of fully developed Addison s disease with cortical tumours of the adrenal gland It is only rarely that evidence is forthcoming of excessive activity of the third function (regulation of salt water metabolism) but high values for serum sodium and chloride and excessive retention of these elements is an occasional accompaniment of the adrenogenital and Cushing s syndromes Over activity of the first function (androgenic) may be present without over activity of the second (metabolic) and vice versa since adrenocortical diabetes has been recorded without other endocrine disturbance (Sprague 1941)

(b) Clinical Classification of Hypercorticalism

The effects of hypercorticalism depend upon age and sex

(1) Pseudo hermaphroditism—prenatal influence
(2) Sexual precocity—childhood
(3) Adrenogenital syndrome—after puberty
(4) Cushing s syndrome—after puberty
(5) Virilism as a complication of acromegaly—after puberty
(6) Feminization of the male—after puberty

(c) Pathology

In all the above conditions either hyperplasia or neoplasm of the adrenal cortex may be responsible for hypercorticalism Where hyperplasia is the lesion it is probably secondary to pituitary hyperfunction the latter producing excessive secretion of the pituitary corticotrophic hormone Such hyperplasia of the adrenal cortex may give rise to multiple adenomas but where a large adenoma or carcinoma is limited to one suprarenal gland and the other suprarenal gland is atrophic then one may postulate a primary neoplasm of the adrenal cortex quite independent of any pituitary stimulus This must also be the case when the neoplasm is in an accessory adrenal gland and both the right and left adrenal glands are atrophic It appears to be a physiological law in endocrinology that excessive amounts in the blood stream of the specific hormone of an endocrine gland either endogenous or exogenous

The cytoplasm of the cells chiefly of the inner layers of the cortex stained a vivid red colour with Ponceau fuchsine in contrast to the blue colour of the normal cells which took the counter stain aniline blue The avidity of the cells for this stain under different clinical conditions is a matter of degree It now became obvious that we were dealing with an altered physiological activity of the adrenal cortical cells in relation to virilism This stain has been corroborated by others in this country and abroad

Vines meanwhile had made an extensive study of this stain and found it was taken up by the acidophil cells of the pituitary the interstitial cells of the testis and the cells of the young corpus luteum In addition a series of some sixty foetuses had been collected and Vines again was able to show that the fuchsine reaction was positive temporarily in the foetal cortical cells of both sexes In the male it was strong between the 9th and 20th week in the female less marked and of shorter duration between the 11th and 17th week At the end of these times it normally disappeared In two foetuses at term the persistence of this stain in the adrenal cortex was associated with marked hypertrophy of the pituitary gland The result of this inquiry to date left the position that a special staining reaction associated with clinical masculinisation of the female had been discovered and that it was present temporarily in the cells of the adrenal cortex of both sexes in the early stages of foetal life

Occasionally an adrenal cortical tumour may arise in an accessory suprarenal gland which latter frequently consists of cortical cells only and may be found anywhere in the abdomen or pelvis apparently being carried down from the embryonic genital ridge with the descent of the gonads into the pelvis In such cases both adrenals may be atrophic or where one adrenal gland is neoplastic the opposite gland is often atrophic Hyperplasia is usually bilateral and it seems reasonable to assume that the hyperplasia is secondary to a pituitary corticotrophic stimulus even in the absence of any further evidence of pituitary hyperfunction The ovaries are hypoplastic or atrophic and it is interesting to note that such a condition of the ovaries may be produced by injecting large doses of testosterone into animals or women The thyroid is usually involuted with flat cuboidal epithelium lining vesicles containing colloid The pituitary is usually normal in uncomplicated cases

An ovarian tumour arrhenoblastoma is occasionally the cause of a virilizing syndrome identical with the adrenogenital syndrome The tumour arises from the medullary part of the ovary (rete ovarii) and is usually of mild malignancy The general appearance is that of a sarcoma but careful microscopic

made The term indicates an adrenal lesion and an interference with sex function and it is always understood that the term applies only to women Another constant factor is the development of hair in the woman in a type of distribution usually met with in man that is hirsutism Thus an adrenogenital syndrome might be defined as a condition of amenorrhoea or oligomenorrhoea associated with hirsutism and due to a hyperplasia or neoplasm of the adrenal cortex This definition avoids the difficulty of some patients being fat and others thin and muscular

(ii) *Pathology* A neoplasm of the adrenal cortex may be adenomatous or carcinomatous All zones of the adrenal cortex may be detected in the neoplasm or the zona fasciculata may be especially prominent on histological examination Similarly hyperplasia of the adrenal cortex may involve all zones or the zona fasciculata may be most prominent Simple histological examination takes us no further than this but embryological considerations and special staining technique offer further contributions The adrenal cortex is mesoblastic and arises from the genital ridge of the embryo from groups of cells which appear to give rise both to the gonads and to the adrenal cortex There is thus an obvious close embryonic relationship which is further emphasized by the adrenal cortex secreting androgens oestrogens and progesterone There is some evidence however that special cells in the adrenal cortex have this function Thus at birth the adrenal cortex is very large and especially the inner zone which however rapidly involutes to normal in the first year of infantile life This zone has been termed by Grollman (1936) the androgenic zone and may be comparable to the X zone in mice of Deanesly and Parkes (see Physiology section) Broster and Vines (1933) also claim that the hyperplastic or neoplastic cortex in the adrenogenital syndrome shows a special affinity for the ponceau fuchsine dye and although this finding is certainly not constant it probably has some validity and I shall therefore quote Broster s recent summary of these findings

> The next stage in the elucidation of the problem of the part which the adrenal cortical cells played in the production of virilism was a most important one In 1933 Broster & Vines published a monograph which drew attention to the fact that Vines had discovered a new stain for virilism It is a differential stain whereby the cortical cells of the adrenal glands removed at operation for virilism assumed quite a different colour from those of the normal glands—the so called Ponceau fuchsine stain

others thin and muscular It is not completely satisfying to suppose that in the former the pituitary is always involved



FIG 37 ADRENOGENITAL SYNDROME Woman aged 28 Hypertrophy of the clitoris and a large excess of male comb growth hormone in the urine the amount of the latter was unchanged some months after unilateral adrenalectomy Note the orbital pigmentation

because (*a*) there may be no further clinical evidence of this (*b*) removal of an adrenal tumour will cause loss of the abnormal fat and (*c*) there is evidence that the adrenal cortex is directly concerned with fat metabolism Thus patients with Addison s disease tend to lose their subcutaneous fat but in laboratory animals adrenal cortical insufficiency is characterized by a slow

search reveals primitive convoluted tubules comparable to the structural development of the normally atrophic left gonad of the hen after removal of the right ovary has led to virilism (Friedgood and Uotila 1941)

(iii) *Clinical* The disorder usually shows itself in the second decade of life and may be a pubertal or adult type In the former although childhood is normal a normal homosexual puberty does not occur There is no menarche or incidence of menstruation the breasts do not develop and the pelvis does not widen All these negative findings suggest that the ovaries never commence to function in the normal female fashion In the adult type there is a normal puberty and some years later menstruation becomes scanty or ceases Intermediate types are met with In both types hair commences to grow on the upper lip and chin and sides of the face and on the legs and thighs It may also be present on the abdomen along the linea alba or in male triangular fashion from the pubis to the umbilicus on the breasts over the sternum and on the back The development of hirsutism appears to depend upon an excessive secretion of androgens by the adrenal cortex but there is also a genetic element which determines the responsiveness of the tissues or the distribution of hair follicles since in some severe cases the trunk nevertheless remains comparatively free from hirsutism

(iv) *Adiposity* Apart from the age of onset there are two distinct clinical types (*a*) adipose (*b*) muscular In the former type the patient may put on several kilograms in weight and the fat is deposited on the face and neck breasts buttocks abdomen the distal portions of the extremities usually remaining comparatively slender The fat depositions are symmetrical and are occasionally painful In the muscular type the pre existing normal fat may disappear the breasts involute and the skeletal muscles sometimes become well developed and powerful The shoulders broaden as in the male and the hips remain comparatively narrow as compared with the shoulders The increased muscular strength may be ascribed to the excessive androgen secretion by the adrenal cortex or it may be more complex than this being the result of several factors the deficiency of which in Addison s disease leads to excessive weakness

It is difficult to understand why some patients become fat and

is slight or absent one wonders whether one is really dealing with a disease or a variety of normality Certainly some hair on

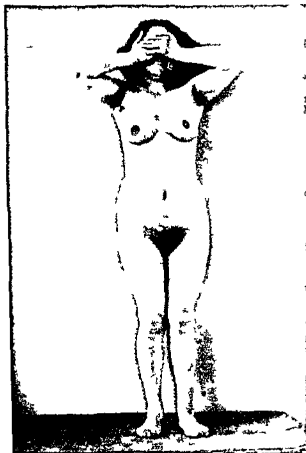


FIG 38 ADRENOGENITAL SYNDROME Woman aged 28 Adiposity is not ma ked the patient approximating more to the male muscular type She alleged that the onset of hirsutism was associated w th increase of strength but this d d not pers st The hair on the body is of male distribution extend ing along the linea alba but the increase in amount is far less than that on the face which is qu te thick Long periods of am norrhoea were interrupted by occasional scanty menstruation Comb growth hormone secreted in excess (For details see *Endocrinology* (1936) xx 364)

the upper lip sides of the face and legs is normal and wide spread and hair along the linea alba is frequently met with in normal women The realization of this would save a great deal

rate of intestinal absorption of fat a decrease in the deposition of hepatic fat and a diminished response to ketogenic agents (Ingle 1943) It has also been suggested by Albright (1941) that with hypercorticalism there is a hypergluconeogenesis from protein with conversion to and storage of fat Whatever the mechanism one must recognize however that there are many intermediate forms between the fat types of adrenogenital syndrome and a complete Cushing s syndrome (see later)

(v) *Carbohydrate metabolism* Diabetes is not a feature of an uncomplicated adrenogenital syndrome and its presence or development is usually regarded as a transition to Cushing s syndrome Nevertheless the carbohydrate tolerance curve in many patients with an adrenogenital syndrome does show a persistence of raised blood sugar values and a delayed return to normal The presence of excessive gluconeogenesis therefore depends upon whether the hypercorticalism is limited to the androgen secreting cells or whether it also affects the corticosterone secreting cells the diabetogenic action of the corticosterones being beyond dispute Clinical evidence makes it extremely probable that the androgen secreting cells are not identical with the corticosterone secreting cells and hyperfunction of the former may be present without hyperfunction of the latter or even vice versa Thus Sprague (1943) observed a woman of 49 years of age in whom severe diabetes (at times requiring the administration of more than 100 units of insulin daily for control) disappeared completely after removal of a huge adrenal cortical tumour and no other endocrine symptoms were present To the knowledge of Kepler and Keating this is the first instance in which diabetes has been the sole symptom of an adrenal cortical tumour

(vi) *Mild or incomplete forms of the adrenogenital syndrome* Whereas well developed forms of adrenogenital syndrome tend to run in families this is especially true of relatively mild forms of this disorder One may also meet with hirsuties in the presence of normal menstruation or scanty menstruation There seems little doubt that these varieties are all manifestations of hypercorticalism and that there is an underlying genetic and ethnological basis Jewesses Celts and Mediterranean people being especially prone In view of the constitutional and familial factor in hirsuties especially when the menstrual disturbance

and not absolute It is difficult to understand why androgen values should be normal in some cases of adrenogenital syndrome since the cortex is obviously hyperactive and one must assume that excretory values do not necessarily reflect secretory values Estimations of serum androgens have not yet been systematically undertaken The steroid index referred to above is a quantitative one but analysis of the urinary androgens shows that there are also some qualitative differences Thus transdehydrosterone appears to be excreted with adrenal neoplasms (Callow 1938) A hyperplastic or neoplastic adrenal cortex al o secretes an excess of progesterone and this is excreted in the urine as pregnanediol or pregnanetriol (Butler and Marrian 1937 Anderson Hain and Patterson 1943) Although a large excess of androgenic hormone in the urine is the u ual finding in women with virilism due to an adrenal tumour it is interesting that in one such case in spite of such a large excess in the urine there was no exce s of such androgenic hormone in the tumour tissue itself (Slot 1936)

Intravenous pyelogram may show renal calyces depressed on one side by an adrenal tumour although a negative radiogram means little A retrograde pyelogram is said to be more likely to give a positive result Perirenal insufflation (Cahill 1942) may reveal the outline of an adrenal neoplasm or of an enlarged hyperplastic gland Through a lumbar puncture needle in the flank attached to a pneumothorax apparatus some 600 c c of air are slowly (20 minutes) allowed to pass by gravity into the perirenal fat and a radiogram is then taken The procedure is comparatively simple but some fatalities have been recorded in America from air emboli m and surgical emphysema has also occurred I have carried out a considerable number of perirenal insufflations without untoward results but the results are not infrequently equivocal and without real value

An adrenogenital syndrome may be caused by an ovarian tumour (arrhenoblastoma) which is not always palpable on pelvic examination so that in severe cases of the syndrome there is much to be said for an exploratory laparotomy when both pelvic organs and adrenal glands may be manually palpated

In the adipose type of adrenogenital syndrome one must bear in mind the possibility of an initial phase of a Cushing s syndrome and an associated or aetiological pituitary lesion

of unhappiness although the attitude of man and woman to hirsuties in the female depends upon unconscious as well as conscious psychological factors Certainly hirsutism in woman is not infrequently accompanied by a severe neurosis and occasionally by a depressive or paranoid psychosis (Allen and others 1939 and 1945) which latter is said to have been cured by unilateral adrenalectomy

Mild degrees of hirsutism may develop during pregnancy after surgical castration or at the climacteric and it is known that the adrenal cortex undergoes hypertrophy in all these conditions Occasionally very severe degrees of hirsutism are encountered at these times and especially may this be the case after bilateral ovariectomy (Kovacs 1932) However the rarity of such considerable disturbance suggests that a pre existing genetic predisposition must be postulated Thornton (1890) described the case of a woman of 36 who developed severe hirsutism after bilateral ovariectomy at the age of 30 At the age of 34 however a left adrenal tumour was discovered and its removal was followed by a return to complete normality

(vii) *Diagnosis* The combination of hirsutism with amenorrhoea or oligomenorrhoea justifies the diagnosis of an adrenogenital syndrome A triad of symptoms may be completed either by an increase of muscular strength and involution of breasts (virile type) or by the development of adiposity (adipose type) Should the latter type develop other features e g diabetes hyperten sion plethora then the diagnosis of Cushing s syndrome may be made and it must be recognized that intermediate stages or types are met with

If an uncomplicated adrenogenital syndrome is diagnosed it *is then necessary to determine whether hyperplasia or neoplasm of the adrenal cortex is present* Estimation of the androgens in the urine is helpful but not necessarily unequivocal (Simpson 1934 Simpson et al 1936 Simpson 1944 and Callow 1938) Measured calorimetrically as milligrams of 17 ketosteroids excreted in 24 hours normal values range between 5 and 15 values in *neoplasm are usually greater than 60 and may be* 600 or more values in the adrenogenital syndrome may be within normal limits moderately raised e g 20 or as high as 80 Since values with neoplasm are occasionally only moderately raised e g 24 the results of biological assay are only suggestive

other or two thirds of each adrenal gland The operation is severe the results still only partial and there is a danger of Addison s disease following too extensive interference However in view of the mental distress that an adrenogenital syndrome may cause and the failure of any hormone treatment including large doses of oestradiol I have referred patients to Broster and others for unilateral adrenalectomy and have seen amelioration result In one such case operated upon by Broster the degree of amelioration amounted to clinical cure Adrenalectomy is more likely to produce amelioration if there has been a latent period of some years between puberty and the onset of the adrenogenital syndrome Del Castillo and colleagues (1939) treated six patients with adrenogenital syndrome by unilateral adrenalectomy One died four developed regular menstruation three showed appreciable lessening of the hirsutism and one *derived no benefit at all They treated two other patients with* massive doses of oestradiol and obtained diminution of headache establishment of menstruation and diminution of hirsutism I cannot concur in the latter finding They considered that their results with oestradiol were better than those obtained from adrenalectomy

Rarely a neoplasm of the adrenal cortex may be bilateral and in one such case under my care (Fig 39) Mr W M Dickson removed a tumour on one side and there resulted a return to normal menstruation The hirsutism has persisted The urinary androgens decreased after operation but have gradually returned to high values 60 steroid units (pre operative 120) There appears to be a neoplasm of the remaining adrenal gland

Where an arrhenoblastoma is the cause of an adrenogenital syndrome its removal will produce a return to normality

(ix) *Appendix A classical case under the care of Gordon Holmes (1924)* The patient was a woman of 26 whose menstruation was regular from the age of 13 to 17 when it ceased At 19 hair appeared on the face and limbs The breasts atrophied and subcutaneous fat disappeared The clitoris became very enlarged Even more striking perhaps than the excessive growth of hair was her general appearance and configuration which strongly suggested masculinity although there still remained evidence that she had been a handsome young woman This was partly due to the sparseness and the distribution of the subcutaneous fat and to the muscular contours of the limbs Her hands were massive her fingers thick and distinctly masculine and the muscles of her arms

N

(viii) *Treatment* Since an adrenogenital syndrome is due to hypercorticalism the logical treatment is removal of the over active suprarenal gland or glands In the case of an adenoma this is comparatively simple and the operation is followed by a return to normality The same is true of a carcinoma although the risk of recurrence or of metastases is obvious Whatever the character of the neoplasm its removal may be followed in the more immediate post operative period by acute hypo corticalism (insufficiency) comparable to the crisis of Addison s disease and death may occur This is due to the fact that the remaining adrenal gland has become involuted or atrophic Therefore it is essential as a prophylactic measure to give cortical extract and desoxycortone just before and for 2 weeks after operation Where bilateral hyperplasia is present the problem is much more difficult Broster (1934 and 1939) is a strong advocate of the efficacy of unilateral adrenalectomy He states that the main features of recovery are the shedding of hair and the return to normal menstruation The acquired hair can be pulled out in bunches with little or no pain within a few days of operation In one case operation was followed by a complete depilation of male hair within a fort night and a period within three days after seven years amenorrhoea He also records the cure of associated neurosis and psychosis (1939 and 1945) and observes a marked fall in the urinary androgens These are indeed very strong grounds for advocating the operation I regret that my own experience does not justify such a degree of optimism Hair is easier to pull out during the more immediate post operative period but it then tends to recur although the texture may be less coarse than before operation Amenorrhoea is frequently followed by menstruation which may be regular and persist so or may occur at infrequent intervals The urinary androgens diminish drama tically and then gradually return to their pre operative values (Simpson et al 1936) Such results namely an immediate amelioration followed by a gradual relapse in the condition is I think what one would expect from an operation which is comparable to hemithyroidectomy for thyrotoxicosis The remaining adrenal like the remaining lobe of the thyroid under goes a secondary further hyperplasia For this reason some surgeons have removed one adrenal gland and one half of the

stood out as they do in a thin but healthy young man This masculine appearance was even more prominent in the lower limbs especially in the buttocks and thighs where the subcutaneous fat that gives the characteristic shape to the female hips was more or less absent At the age of 26 pain in the right side drew attention to a palpable adrenal tumour which was removed The result after operation was that 36 days after operation she menstruated for the first time for nine years and about the same time the hair on the face and somewhat later that on the trunk began to fall Six years later she reported that menstruation had been regular ever since operation and that the abnormal hair of the face and limbs had entirely disappeared The clitoris had shrunk to normal size her breasts had again developed and feminine subcutaneous fat returned It was recorded that the adrenal tumour weighed 1 075 gm and that its cells resembled those of the zona reticularis

(f) Pituitary Adrenogenital Syndrome

The existence of virilism as a complication of acromegaly is rare but recognized and is illustrated in this book (Fig 9) The hirsutism may not develop until several years after the acromegaly has been clinically obvious Virilism is also a complication or feature of Cushing s syndrome when the latter is apparently due to a basophil adenoma and can be cured by destructive therapy (radiation or radon seeds) localized to the pituitary gland Further whenever an adrenogenital syndrome is due to hyperplasia and not a neoplasm of one adrenal gland all physiological knowledge justifies the hypothesis of a pituitary adrenocorticotrophic stimulus

Nevertheless I wish to draw attention in this separate section to a clinical entity which is really a mild form of virilism complicating acromegaly but which presents itself as a simple adrenogenital syndrome and is only differentiated from the remainder of this group when symptoms of over activity of the pituitary growth hormone are looked for The patients are big boned tall for women and the male members of their family are usually 6 feet in height or more They have protuberant jaws (prognathism) and their hands and feet are large The muscular development is good and their strength normal or above normal Their skill at games is usually good Some degree of adiposity may be present but it is rarely extreme and may be absent altogether Their skin tends to be blotchy owing to the sweat and sebaceous glands being over active and acne

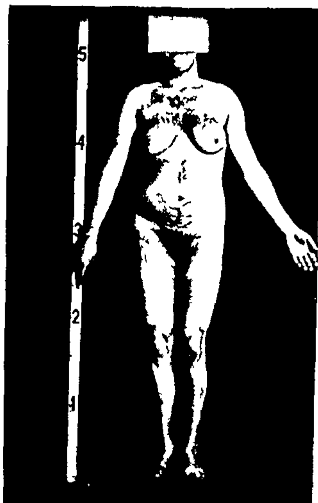


Fig 39 Virilism Woman aged 21 at time of photograph Menstruation was normal from age 14 to 16 when amenorrhoea developed together with hirsutism deepening of voice and increase of weight Radiography after uroselectan showed a right adrenal tumour which was removed (age 21) after which menstruation became regular once more but hirsutism persisted The 17 ketosteroids were very high (143 mg per day) before operation and although reduced by more than 50 per cent still remain very high namely 60 mg per day as compared with the normal of 5 to 12 mg This explains the persistent hirsutism 8 years after operation and the probability of adrenal hyperplasia or neoplasm in the remaining gland A primary pituitary stimulus is postulated

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may be troublesome Of course one meets thousands of such women in ordinary life and the hair on their arms and legs and along the linea alba, although more than average may be regarded as within normal limits In some however it is sufficiently excessive to cause much anxiety and is also present on the sides of the face lips and chin breasts and chest The hair of the head tends to be dry and coarse Menstruation may continue normally or may become scanty or irregular or complete amenorrhoea may supervene In some patients anovular bleeding is present and there is an absence of the gonadotrophic luteinizing hormone If pregnancy occurs the syndrome is exacerbated and lactation may be profuse and persistent

In one patient of this type under my care (Fig 39) an adrenal tumour was present in the right side and it is not yet established whether a tumour or hyperplasia of the adrenal cortex is present on the left side This however is an unusual complication of the common pituitary adrenogenital syndrome described above

(g) *Feminization*

This condition is the counterpart of virilism in females and might be considered as an adrenogenital syndrome in man although this term (adrenogenital syndrome) is usually limited to the disorder in woman From an aetiological point of view it should be regarded as an expression of hypercorticalism in the male whether due to neoplasm or hyperplasia of the adrenal cortex the latter also occurring with Cushing s syndrome This clinical result of hypercorticalism is however only intelligible when it is realized that hypercorticalism in the male results in excessive secretion of oestrogens whereas in the female there is excessive secretion of androgens Why this should be so is not known and the matter is fully discussed in the previous section on the adrenogenital syndrome A further unexplained anomaly is that whereas adrenal cortical tumours in the adult male secrete a great excess of oestrogens such tumours in boys secrete an excess of androgens and produce sexual precocity (which see) It is probable that excessive secretion of progesterone by adrenal tumours occurs in both sexes

Incomplete feminization manifested by gynaecomastia is produced by a number of conditions described below

Definition Feminization is a condition in the male character

ized in its fully developed form by atrophy of the testes loss of libido and potency development of the glandular tissue of the breast and deposition of fatty tissue The latter condition is not invariably present and in any case the fat may be lost if a malignant adrenal tumour is present

Incidence Feminization is a rare disorder only seven cases associated with an adrenal cortical tumour having been adequately described

Pathology An adrenal cortical tumour which may be adenomatous at first but later becomes malignant is the most definite cause (see also Cushing s syndrome in the male) The glandular tissue of the breasts undergoes hyperplasia The testicular tubules undergo hyalinization and the interstitial cells become fibrosed

Clinical Cases have been described by Bittorf (1919) Zum Busch (1927) Holl (2) (1930) Lisser (1936) Simpson and Joll (1938) and Poholm and Teilum (1942) In view of the rarity of the disorder the clinical description of four cases will be given

Holl s two cases The first was a lad of 15 who for 2 months had observed progressive enlargement of the breasts which projected in bud like fashion like those of a young girl The nipples were deeply pigmented The suprapubic hair was of feminine type with horizontal border Death followed removal of a malignant cortical tumour

Holl s second case was a male of 44 years of age with two children The breasts slowly enlarged with some pain and the nipples became large and pigmented The testes and penis became smaller libido was lost and sexual intercourse ceased The patient became fat and his face took on a soft feminine appearance The unique feature of this case, however is that removal of an adenomatous cortical tumour was followed by a return to complete normality

Simpson and Joll s case This was a physician of 34 in which the presenting symptom was pain in the left scapula and hypochondrium However in retrospect it was seen that two years before there had been enlargement of the breasts with general increase of fat deposition and one year before diminution in size of the penis and testes with loss of libido and potency The adiposity however only lasted some months and was followed by loss of weight A large malignant cortical tumour was removed from the left side and incomplete clinical improvement ensued namely decrease in size of breasts and partial recovery of libido and potency This was only temporary and ceased with the development of hepatic and visceral metastases from which the patient died The interesting feature of this case however was the biological assay of the urine for androgens and oestrogens Burrows (1936) found that the oestrogens were excessively high at the time of operation fell

to values below normal after operation and subsequently increased to very high values (3 000 units per litre) with the development of metastases (de Fremery 1938) Burrows and colleagues (1936) stated that an attempt to isolate the oestrogenic hormone from the urine has not been successful but the results are consistent with the view that the hormone is oestrone de Fremery found a slight increase above normal of androgens as measured by the comb growth method No pregnanediol assays were done but it seems probable from our experience of such tumours in women that progesterone was secreted in excess by the tumour

The above biological findings were confirmed by Roholm and Teilum (1942) in their patient and illustrates the biological mechanism of the production of symptoms The essential feature is the large excess of oestrogens which (1) inhibit the secretion of pituitary gonadotrophic hormone with resulting involution and atrophy of the testes and (2) produce hyperplasia of the rudimentary breast tissue this action possibly being reinforced by the excessive secretion of progesterone

Treatment Removal of an adrenal tumour where present is the obvious treatment and where this is benign or in the early stages of malignancy complete recovery may ensue

(h) Gynaecomastia

Definition

This term derived from the Greek means breast of a woman It may be defined as excessive development of the breast tissue of one or both breasts in a man often associated with discomfort or pain and rarely associated with mammary secretion Although the condition is usually bilateral one breast is not infrequently affected to a greater extent than the other and the condition may be limited to one breast Aetiological factors therefore are qualified by local responsiveness of tissue (mammary in this case) as not infrequently happens in endocrinology

Aetiology

Experimental evidence indicates that several hormones may be involved in producing mammary development Perhaps of greatest importance are oestradiol which produces development of the mammary duct system and progesterone which stimulates the mammary alveoli It has been thought for some time that the only role of the pituitary was to initiate and maintain lactation by virtue of its hormone prolactin Since however oestradiol and progesterone are without effect on the breast

tissue in hypophysectomized animals it has been necessary to postulate other pituitary hormones, Mammogen I and Mammogen II which are thought to be released respectively by oestradiol and progesterone and produce or reinforce actions attributed to these ovarian hormones respectively (Gomez and Turner 1938 1942) *Testosterone may also produce some enlargement* of the mammary duct system although large doses inhibit mammary development Desoxycortone an adrenal cortex hormone somewhat unexpectedly produces gynaecomastia in mice (Heuverswyn and others 1939) and both desoxycortone and cortical extract may have a similar effect on the breast tissue of man (Lawrence 1943 Edwards and others 1938) Mammary secretion may be produced by prolactin or by oestradiol the latter effect possibly by releasing prolactin from the pituitary gland

Pathology

The histological picture is identical with the gland in normal women but adenomatous formation and fibrosis may be met with and sometimes the picture is similar to that of chronic mastitis in women

Clinical

(1) *Idiopathic* Sullivan and Munslow (1942) observed five cases in one division of the American Army in which there was no obvious cause The patients complained that wearing a pack produced discomfort and pain

(2) *Puberty* Boys may have swelling of the breasts at puberty and this may last for months or longer Nathanson (1942) records Jung and Shafton s observation that in 1 000 examinations of adolescents they found palpable mammary tissue so frequently as to regard it as an integral part of the process of puberty Nathanson investigated such cases biologically and found a relative increase in the proportion of urinary oestrogens to 17 ketosteroids

(3) *Adrenal cortical tumours* See above

(4) *Cushing s syndrome in man* See page 103 Pituitary section

(5) *Atrophy of the testis* The atrophy may be caused by syphilis gonorrhoea mumps tuberculosis or leprosy One

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and casts and albumen were present in the urine The hypertension as well as some abdominal lineae distensae and slight osteoporosis of bones were features suggestive of Cushing's syndrome The genitalia were infantile and puberty had not developed the initial diagnosis being dystrophia adiposo genitalis The breasts were not enlarged A large adrenal cortical tumour was discovered by urography and the patient died 10 hours after its removal although large amounts of cortin were given

At autopsy both adrenals were present and both were hypoplastic being one fifth of the normal size and the cortex was thin and without lipoids The removed adrenal was an accessory gland Serial sections of the pituitary gland showed few basophil cells in the anterior lobe and a circumscribed slight augmentation of basophil cells in the posterior lobe No mention is made of hyalinization of basophil cells but if such were present it is difficult to conceive of a primary pituitary lesion in view of the atrophy of both adrenal glands One cannot exclude the possibility of a primary adrenal tumour in an accessory adrenal gland bringing about by its secretion secondary changes in the pituitary gland

2 *Schill's case (1936)* This concerned a man of 68 who a few years previously had lost all of his hair but without having experienced any symptoms of bodily disorder Six months after this he experienced haematuria and urological examination disclosed a tumour of the left kidney This was removed and on section the tumour was seen to have the typical structure of a hypernephroma The tumour cells were arranged in long narrow columns mostly parallel Following the operation hair grew on the head eyebrows moustache and beard areas This case is very unusual and difficult of explanation and the histological findings are probably not absolutely indicative of an adrenal cortical tumour It is however a case to remember and further knowledge may elucidate the mechanism of the symptomatology

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might postulate that the resulting hypertrophy of the adrenal cortex results in an excessive secretion of oestrogens (Edmondson et al 1939) or that there is a disproportionate secretion of oestrogens compared with androgens

(6) *Testicular neoplasms* Gynaecomastia has been described as a result of teratoma or chorionepithelioma of the testis Here too there is probably an absolute or relative excess of oestrogens

(7) *Acromegaly* Gynaecomastia is an occasional complication of acromegaly in man and there may even be mammary secretion (Roth quoted by Parkes Weber 1944) Theoretically the pituitary might be directly responsible or indirectly via secondary adrenal cortical hyperplasia

(8) *Frohlich s syndrome* If true gynaecomastia is present its aetiology may be comparable to that associated with atrophy of the testis (see above) More usually there is excessive deposition of fat in the mammary area simulating breast tissue

(9) *Atrophy of the liver* Over 70 cases have been reported in the literature and according to Edmondson and co workers (1939) the liver is no longer able to carry out its normal function of inactivation of oestrogens They found an increased oestrogen excretion in the urine

(10) *Stilboestrol manufacture* A proportion of male workers develop gynaecomastia

Treatment

Although relative excess of oestrogens to androgens has been reported the administration of testosterone is not really of use (Dunn 1944) In fact apart from such cases where an adrenal tumour may be removed hormone treatment is rarely satisfactory Surgical removal of breasts should be undertaken where there is much pain or psychological disturbance or for cosmetic reasons

(i) Unusual Cases of Adrenal Cortex Tumours in Males

There is a tendency to permit unusual cases which disturb current theories to fade from memory I therefore append brief notes of two such cases

1 *Josephson's case (1936)* This relates to a boy of 17 who was very thin until the age of 14 and then became very fat and dyspnoeic His blood pressure was 220 mm of mercury systolic and 130 diastolic

CHAPTER XVII

HYPOCORTICALISM—ADDISON'S DISEASE

(i) Definition

A CONDITION of adrenal cortical insufficiency, usually due to tuberculosis or atrophy of the adrenal cortex, and characterized by pigmentation, hypotension, weakness, wasting and anorexia

(ii) History

Addison's disease was first described in 1849 by Thomas Addison, physician to Guy's Hospital, in an address to the South London Medical Society. The paper was entitled On Anaemia Disease of the Suprarenal Capsules, since he had not then differentiated the idiopathic anaemia which was subsequently named after him. In 1855, however, assisted by his junior colleague Samuel Wilks, he produced his clinical monograph *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*. William Hunter in 1909 suggested the term Addison's disease

(iii) Aetiology and Pathology

The disease occurs in both sexes, is most frequent in the third and fourth decade, and is rare in children and old age. Tuberculosis is responsible for 70 per cent of cases and idiopathic atrophy for 25 per cent. Other causes are syphilis, amyloid disease, haemorrhage and malignant neoplasm. The latter in rare instances may produce the disease by involving the nerve supply rather than the actual gland. Tuberculosis may be limited to the adrenal glands, but usually other tuberculous lesions, active or healed, are found in the lungs and bronchial glands, or in the abdomen, or the cervical glands, or the bones. The cortex and medulla are almost entirely replaced by fibro-caseous tuberculous tissues with areas of calcification and here and there islets of regenerated cortical cells. Microscopically, encapsulated areas of homogeneous necrosis are visible with few tubercles, and in other parts of the gland more proliferative lesions with many tubercles, giant cells, endothelial cells, fibroblasts and lymphoblasts

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pensatory hypertrophy may be detected The histological picture bears a close resemblance to a toxic necrosis as for example occurs in the liver than to a simple atrophy The medulla is of normal size and pattern, except perhaps for some lymphocytic infiltration The cause of the atrophic process is unknown and it has been definitely correlated with an antecedent history of influenza or specific fever

Lymphatic hyperplasia involving the glands thyroid spleen and thymus is a frequent feature The thymus may be large and persistent in the adolescent The heart is small and shows brown atrophy The kidneys may be normal or congested or the tubules may have undergone degeneration There is a reduction in the percentage of basophil cells in the pituitary gland as also occurs after experimental bilateral adrenalectomy The testes and ovaries may be quite normal but degenerative or atrophic changes are also met with

(iv) Clinical Features

The first manifestation of Addison's disease may be an acute crisis but more usually the onset is insidious The classical description of Addison (1855) constitutes an excellent clinical picture

The patient in most of the cases I have seen has been observed gradually to fall off in general health he becomes languid and weak indisposed either to bodily or mental exertion the appetite is impaired or entirely lost the whites of the eyes become pearly the pulse small and feeble or perhaps somewhat large but excessively soft and compressible the body wastes without however presenting the dry and shrivelled skin and extreme emaciation usually attendant on protracted malignant disease slight pain or uneasiness is from time to time referred to the region of the stomach and there is occasionally actual vomiting which in one instance was both urgent and distressing and it is by no means uncommon for the patient to manifest indications of disturbed cerebral circulation We discover a most remarkable and so far as I know characteristic discoloration taking place in the skin—sufficiently marked indeed as generally to have attracted the attention of the patient himself or the patient's friends This discoloration pervades the whole surface of the body and is commonly most strongly manifested on the face neck superior extremities penis and scrotum and in the flexures of the axillae and around the navel It may be said to present a dingy or smoky appearance or various tints or shades of deep amber or chestnut brown and in one instance the skin was so universally and so deeply darkened that but for the features the patient might have

In idiopathic atrophy the glands may be quite small and difficult to find On microscopic examination it can be seen that the pathological process is almost entirely limited to the cortex thus



Fig 40 Addison's Disease Radiogram showing calcification of a tuberculous adrenal gland

confirming the experimental evidence that destruction of the cortex and not the medulla is responsible for the syndrome of adrenal gland insufficiency The cortical layer is very thin and almost entirely replaced by distended capillaries lying in a sparse delicate connective tissue infiltrated with lymphocytes plasma cells and histiocytes Small areas of surviving cortex and large atypical cells in the process of regeneration and com

defect of colouring matter in these parts Indeed as will appear in the subsequent cases this irregular distribution of pigment cells is by no means limited to the integument but is occasionally also made manifest on some of the internal structures We have seen it in the form of small



Fig 41 (*b*)

(*b*) The patient's hands The palmar aspect of the hand is free from pigmentation except at the flexor creases

black spots beneath the peritoneum of the mesentery and omentum—a form which in one instance presented itself on the skin of the abdomen This singular discoloration usually increases with the advance of the disease the anaemia languor failure of appetite and feebleness of the heart become aggravated a darkish streak usually appears upon the commissure of the lips the body wastes but without the emaciation

been mistaken for a mulatto In some cases the discoloration occurs in patches or perhaps rather certain parts are so much darker than others as to impart to the surface a mottled or somewhat chequered appearance



Fig 41 (a)

Fig 41 Addison s Disease (a) Note the emaciation and pigmentation the latter chiefly on exposed areas

and in one instance there were in the midst of the mottling certain insular portions of the integument presenting a blanched or morbidly white appearance either in consequence of these portions having remained altogether unaffected by the disease and thereby contrasting strongly with the surrounding skin or as I believe from an actual

associated with nausea and vomiting Constipation is frequently met with but intermittent periods of diarrhoea may be troublesome and sometimes intractable A drastic purge may precipitate a crisis Hypochlorydria or achlorhydria is frequently found Various types of abdominal pain may simulate intestinal colic gastric ulcer gastric perforation gall bladder disease and renal disease This last is suggested by the pain in the loin due to the underlying tuberculous adrenal and tenderness in the costovertebral angle is often present Irritation of the overlying diaphragm and adjacent pleura produces pain referred to the shoulder (diaphragmatic pleurisy) and round the costal margin the pain sometimes being very severe

(vii) Cardiovascular System

Subnormal systolic and diastolic blood pressure is characteristic e g 90 and 50 mm of mercury respectively This may fall still farther on assuming the erect position producing thereby a feeling of faintness or actual syncope In the initial stages of the disease the blood pressure may be normal or rarely above normal In the more severe phases of the disease and especially in a crisis there is an acute fall of blood pressure and the pulse becomes rapid and feeble In addition there is a considerable degree of haemoconcentration the veins are collapsed and difficult to enter by venepuncture and the venous blood is viscous

(viii) Respiratory System

Disorders of rhythm and sighing respirations are not uncommon in the more severe phases of the disease There is also a susceptibility to respiratory infection and the supervention of bronchitis or pneumonia may precipitate a crisis and prove fatal Ante mortem evidence of pulmonary tuberculosis is infrequent and the incidence of Addison s disease in tuberculosis clinics or sanatoria is small

(ix) Muscular System

Muscular weakness and easy fatiguability are characteristic Asthenia affects all the muscles and not one special group of muscles as in myasthenia gravis There may be considerable muscular wasting and creatinuria The latter in contrast with the creatinuria of myasthenia gravis disappears on treatment

and dry harsh condition of the surface so often observed in ordinary malignant disease the pulse becomes smaller and weaker and without any special complaint of pain or uneasiness the patient at length sinks and expires

(v) Pigmentation

The pigmentation is an increase of the normal melanin pigment of the basal layers of the epidermis It has been suggested that the precursor of melanin is dioxyphenylalanine a derivative of tyrosine and that the diseased adrenal glands unlike the normal glands are unable to convert dioxyphenylalanine into adrenaline This dopa theory was propagated at a time when Addison's disease was wrongly believed to be due to a deficiency of adrenaline The pigmentation is especially intense in areas exposed to light pressure and irritation The palms of the hands and soles of the feet, however escape pigmentation except for the creases at the interphalangeal joints Almost pathognomonic of the disease is the pigmentation of the mucous membrane of the mouth involving the inside of the cheeks the inner lips gums and posterior aspect of the palate In some patients however the pigmentation is limited to the skin Some degree of desquamation of the latter is not uncommon As Addison himself pointed out a leukodermic type of pigmentation is occasionally met with and the correctness of the diagnosis in such a case has been substantiated by post mortem examination

Although patients tend to become more pigmented in phases of relapse and less pigmented in periods of improvement the degree of pigmentation is not necessarily a measure of the severity of the disease In fact deep pigmentation may be present for some time before any other major manifestation of the disorder On the other hand precipitate onset and an acute downhill course may be met with in patients with little or no pigmentation This is especially true in people of naturally fair skin For the above reasons the pigmentation has even been regarded as protective and as exerting a compensatory hormone function There is however no conclusive evidence to support this theory

(vi) Gastro intestinal Disorders

Anorexia especially for fatty foods is usual often being

excretion of urine is diminished and may fail altogether the urine containing granular casts and albumen the blood urea and non protein nitrogen being raised above normal The failure of renal function is partly due to circulatory failure and a disturbance of salt and water metabolism but the kidneys themselves may undergo degenerative changes The adrenal cortex may directly influence renal function

(xiii) Genital System

In the more severe phases of the disease impotence and amenorrhoea are not uncommon but in some patients menstruation may continue quite normally until death It is probable that the adrenals influence the gonads via the pituitary Pregnancy is rarely met with but two successful pregnancies in one patient with live normal babies have been recorded (Simpson 1946) In the initial months of pregnancy the patient may even appear to improve but later on the adrenal insufficiency is aggravated Occasionally the first indication of the disease is given in pregnancy by an excessive degree or persistance of pigmentation which as a temporary manifestation may be physiological This pigmentation may be followed by a latent period of months or years before the complete clinical picture develops Symptoms may be aggravated at the time of menstruation or at the climacteric The post climacteric phase however may herald the onset of spontaneous recovery the latter being of appreciable degree or even complete

(xiv) Carbohydrate Metabolism

Porges (1910) was the first to point out that a low blood sugar occurred in Addison s disease Wadi (1928) described hypoglycaemic attacks in a man of 24 a few days prior to death His blood sugar concentration was 71 mg per cent in the more chronic phase but 43 mg and 36 mg in hypoglycaemic attacks that were relieved by intravenous glucose The diagnosis of Addison s disease was confirmed at autopsy the suprarenal gland being almost completely destroyed by tuberculosis Snell and Rowntree (1929) found that hypoglycaemia was present in the terminal phases In the writer s experience (1932) the blood sugar concentration in Addison s disease may be normal or subnormal in the more chronic phases of the disorder but

with cortical extract (Simpson and Bernhardt 1932) Cramps of the calf muscles are sometimes met with and may be due to hypochloraemia In the early stages of the disease muscular strength may be appreciably affected Hypoparathyroid tetany is a rare complication

(x) Nervous System

Inertia lassitude and apathy are common but there may be periods of restlessness excitability and insomnia Sometimes the patients tend to lie curled up in bed or to sink down beneath the covering Involuntary cries and grimaces and later delirium may precede a crisis Negativism contrariness and pessimism may be features of the more chronic phases but adequate therapy restores the mental outlook to normality

(xi) Blood

There is a concentration of the blood and a diminution in the plasma volume This is accentuated by diarrhoea and vomiting but also occurs in their absence There may be an increase in the red cell count but with the disappearance of the anhydraemia under treatment the number of red cells becomes normal or an occult secondary anaemia may be revealed A slight hypochromic microcytic anaemia is present in about half the cases in some it is very severe It responds to iron and is probably related to the achlorhydria The anaemia however may be due to the deficiency of adrenal cortex as cortical hyperplasia and neoplasm is associated with polycythaemia Diminution in the total number of leucocytes may be slight or considerable and as there is also a relative lymphocytosis a possible connexion with agranulocytosis has been mooted Eosinophilia has been observed in some patients This decrease in neutrophiles and the increase in lymphocytes and eosinophils is specific as the opposite changes occur in Cushing's disease (De La Balze Reifenstein and Albright 1946)

(xii) Renal System

In the less severe phases of the disease it is rare to find any abnormality of the urine although renal function tests may give subnormal values In a crisis and to a less extent in subacute phases of the disease renal function is severely impaired the

to normal values Patients treated with desoxycortone only which has no influence on carbohydrate metabolism may have



FIG 4 (b)

(b) The patient's hands Note the pigmentation on dorsum and on the ventral aspect of the forearm up to the wrist The palms escape except for the flexor aspect of the joints

persistently low blood sugar values and rarely hypoglycaemic crises Eppinger Falta and Rudinger (1909) found an increased carbohydrate tolerance The writer (1932) recorded tolerance curves which tended to support this but also indicated the complicating factor of retarded intestinal absorption Since

hypoglycaemic values are frequently met with in crisis Under treatment with cortical extract the blood sugar concentration

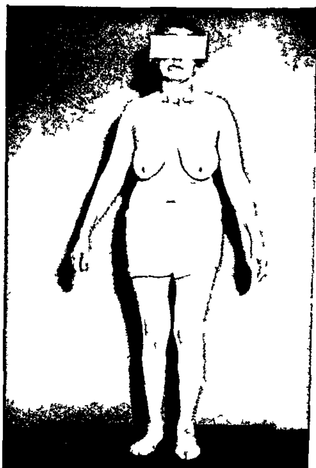


Fig 4 (a)

Fig 4. Addison's Disease (a) Woman aged 36 Note the pigmentation on the areas exposed to the air or to friction e g face and hands waist line lower sternum and knees

will rise rapidly in acute phases but in subacute or chronic phases the low blood sugar may persist for a few weeks or months or longer One patient remained in good health for years with a blood sugar concentration between 60 and 65 mg per 100 c c but more usually there is a tendency to approximate

subacute phases or in a crisis Although intermittent pyrexia is not infrequent the temperature in Addison s disease tends to be subnormal and the patient is sensitive to cold This may be related to the disturbance of carbohydrate metabolism Adrenalectomized animals die when exposed to cold unless treated with corticosterone or extracts containing it

(xvi) Mineral Metabolism

The adrenal cortex has a profound influence on mineral metabolism and water balance Loeb (1932) found in patients with Addison s disease that the serum sodium and chloride concentrations were below normal and the serum potassium above normal Thus the serum concentration of sodium might be only 290 mg per 100 c c compared with a normal of 325 mg that of chlorine 330 mg compared with a normal of 355 mg that of potassium 24 mg compared with a normal of 20 mg

Expressing plasma electrolytes in terms of milli equivalents is probably more scientific the milli equivalent of any substance being its equivalent weight in milligrams and being obtained by dividing the number of milligrams of substance in one litre by the equivalent weight (atomic weight in the case of monovalent elements half the atomic weight in the case of divalent elements) Thus a normal serum value of 355 mg of chlorine per 100 c c or 3 550 mg per 1 000 c c equals 100 m eq per litre the atomic weight of chlorine being 35 5 Allott (1945) gives the following values

	Mean normal value as often expressed	*Value s per litr*	*Divide by equiv ue ght*	*Mean normal valu in m eq per lit*
Chlorine				
(as chlorine)	355 mg /100 c c	3 550 mg /lit	35 5	100
(as sodium chloride)	585 mg /100 c c	5 850 mg /lit	58 5	100
Sodium	325 mg /100 c c	3 250 mg /lit	23 0	141
Potassium	20 mg /100 c c	200 mg /lit	39 1	5

Loeb also observed that there was an increased excretion of sodium and chlorine in the urine with a negative balance for these elements and an increased retention of potassium These results were confirmed repeatedly by subsequent observers (Harrop 1933 Allott 1936 &c) Usually the values for sodium and chlorine are subnormal even in the more chronic phases of

adrenaline produces a rise of blood within 20 minutes of injection it might be postulated that the low blood sugar in Addison's disease is due to a deficient secretion of adrenaline This however is not a logical conclusion and low blood sugar concentrations are met with in patients in whom ultimate autopsy showed the cortex only to be destroyed and the medulla intact Further it has been noted in the physiological section that cortical extract alone or corticosterone will restore the disturbed carbohydrate metabolism of the adrenalectomized animal to normal

It is interesting to note that diabetes mellitus may be associated with Addison's disease either preceding or following the first manifestations of the latter disease In four such cases the diagnosis of Addison's disease was not made in life the pathological lesions at post mortem being tuberculosis (1) atrophy (1) haemochromatosis (2) Arnett (1927) and Simpson (1932) described one case each in which the diagnosis was obvious in life and in which autopsy showed atrophy of both the adrenals and the pancreas I have since had another male patient under my care who developed Addison's disease while under treatment by Dr R D Lawrence for diabetes mellitus The insulin *requirements were drastically diminished by the complication* of the suprarenal insufficiency the latter being treated by desoxycortone implantations Both conditions have now been present for some years Thorn and Clinton (1943) have described a case of Addison's disease in which diabetes supervened and in which the diabetogenic action of 11 dehydrocorticosterone could be demonstrated Snell and Rowntree (1929) described a case in which there was an additional complication of exophthalmic goitre (Since writing the above a third male patient under my care with Addison's disease has developed diabetes mellitus)

Although experimental evidence confirms the fundamental role of the adrenals in carbohydrate metabolism and although patients with adrenal insufficiency may die in hypoglycaemic coma it is equally true that the mere maintenance of normal blood sugar values by intravenous glucose will not in itself prevent death in Addison's disease

(xv) Basal Metabolism

This is usually normal or slightly subnormal in the more chronic phases of the disease but may fall considerably in the

therapy with cortical extract also leads to a crisis Diarrhoea is one of the features of adrenal insufficiency especially in more severe phases but it is also true that excessive diarrhoea produced by a drastic purge in a constipated patient may prove intractable and be the immediate precursor of a crisis



FIG 43 ADDISON'S DISEASE Extreme pigmentation of the hands in a girl of 18 with acute Addison's disease showing excessive deposition of melanin on the dorsal aspect of the finger joints

Frequently there is no warning of a crisis which comes on with great suddenness but there are significant symptoms of a relatively minor character which in the writer's experience can be regarded as of a warning nature Thus the patient may yawn a great deal and stretch himself frequently perhaps uttering involuntary cries or monosyllabic sighs The onset and persistence of hiccoughs is an adverse sign A susceptibility to conjunctivitis should not be disregarded and photophobia may be ominous An increased sensitivity to cold or actual shivering especially if the patient curls himself up well beneath the blankets and refuses to answer questions should quite properly give rise to anxiety as to the state of adrenal insufficiency In this stage also there may be an inexplicable tendency to make unpleasant grimaces and also a degree of irritability and negativeness Some of these features are due to hypoglycaemia

the disease although they tend to fall much lower in periods of relapse and especially in a crisis The serum potassium however is rarely appreciably raised unless the patient is seriously ill and although this retention of potassium is usually regarded as being secondary to the abnormal loss of sodium the effect of desoxycortone in depressing potassium appears to be specific (Simpson 1944) Allott (1936) found that increased values for potassium might be found in Addison s disease in the absence of any change in the serum sodium and chlorine although in the writer s experience this is not the usual finding

The disturbance of mineral metabolism is partly responsible for the rise in blood urea that occurs in the more severe phases of Addison s disease and the administration of salt only will often produce a return of blood urea concentration to normal

McCance (1936) *produced in normal people many of the symptoms of Addison s disease by increasing the excretion of salt through sweating and at the same time giving a diet low in salt content* The serum values for sodium and chlorine were comparable to those found in Addison s disease and the blood urea rose above normal There was however no rise in the concentration of potassium in the serum

(xvii) *Crisis*

The term crisis in Addison s disease is applied to an acute *phase of the disorder in which the patient is collapsed and sometimes* even comatose Death is imminent unless active specific therapy is available The patient may pass from a state of chronic insufficiency into a crisis in the absence of any precipitating cause More usually the incidence of intercurrent infection to which Addison patients are especially susceptible is an important factor On the other hand it should be remembered that patients inadequately treated and therefore liable to enter upon a crisis are much more liable to contract an intercurrent infection than are patients receiving adequate therapy Extra exertion or even anxiety in the absence of increased dosage of cortical extract might lead to a crisis It is obvious that a premature reduction of a dosage of cortical extract or its temporary unavailability would lead to the manifestations of acute insufficiency A degree of shock with or without surgical interference in the absence of adequate supplementary specific

bility to the tubercle bacillus In patients over 50 years of age metastatic carcinomatosis may rarely involve both adrenal glands but tuberculous and atrophic adrenal lesions also occur in older people Some pigmentation of the skin may be present in carcinomatosis without any gross lesion in the adrenals In a man of 43 under the care of Dr Cawadias (1946) and seen by the writer the cause of Addison's disease of 3 years duration was found to be primary carcinoma of both adrenal glands (cortex) The sedimentation rate was 70 mm in one hour

In Simmonds's cachexia many of the features of Addison's disease are met with but pigmentation of the skin in the former condition is never more than slight and patchy and pigmentation of the mucous membranes does not occur Further failure of sex development or of established sex function is an early and essential feature whereas in Addison's disease sexual function may persist normally or fail in the more severe phases of the disease and rarely if ever is the secondary sexual hair lost in Addison's disease There is a haematological and chemical response to cortiotrophic hormone (which see) in Simmonds's but not in Addison's disease

Although pigmentation of the skin is almost invariably a feature of Addison's disease it may be very slight or even undetected in fair skinned people especially when the onset is acute Pigmentation of the mucous membrane is usual but not invariable Rarely the pigmentation of the skin is indistinguishable from that of idiopathic leucoderma If pigmentation occurs in the mucous membrane of the mouth as well as in the skin it is almost invariably due to adrenal insufficiency Such pigmentation has been said to occur in pernicious anaemia and Addison himself originally confused the two diseases but neither the writer nor two colleagues who have examined hundreds of patients with pernicious anaemia have ever seen pigmentation of the mucous membrane in this disease although pigmentation of the skin certainly does sometimes occur In three other diseases pigmentation of the mucous membranes is said to occur chronic arsenic poisoning abdominal carcinoma and haemochromatosis In the first and the last the adrenal glands are infiltrated with arsenic and haemosiderin respectively as are the other organs and the pigmentation when present is therefore an expression of adrenal insufficiency In abdominal

which may be the immediate cause of death if unrelieved by glucose (Simpson 1934)

As regards the chemical indication of a crisis this is somewhat variable and not necessarily reliable Thus normal values for serum sodium and chlorine and blood sugar and urea although generally reassuring cannot be interpreted as guaranteeing *freedom from imminent crisis* especially if associated with a poor clinical condition On the other hand severely depressed values for serum sodium and chlorine e g 275 mg and 290 mg per 100 c c respectively frequently herald a crisis A raised serum potassium e g 28 mg per 100 c c is a serious indication The blood sugar is not infrequently normal in subacute adrenal insufficiency but should values below 65 mg per 100 c c be obtained an incipient crisis might well be anticipated A *normal blood urea is by no means an absolute indication of* adequate therapy but a blood urea above 50 mg per 100 c c often indicates adrenal insufficiency of some severity

In a crisis the patient is obviously dehydrated the veins collapsed and the venous blood viscous Rowntree Brown and Roth (1929) found direct evidence of anhydraemia since the blood volume and plasma volume were reduced The concentration of serum proteins was found to vary between 8 3 and 9 9 mg per 100 c c in crisis compared with values between 5 0 and 7 9 mg in patients in good condition (Rowntree Green Swingle and Pfiffner 1931) There was also a decrease in the alkali reserve of the blood These findings have been frequently corroborated

(xviii) Associated Endocrine Disorders

Addison s disease may be complicated by myxoedema hyperthyroidism or diabetes mellitus

(xix) Diagnosis and Differential Diagnosis

(*a*) *Clinical* A combination of weakness loss of weight anorexia nausea or vomiting low blood pressure and pigmentation of the skin and mucous membrane is strongly indicative of Addison s disease especially when no other organic lesion can be detected A previous history of abdominal cervical bone or pulmonary tuberculosis or of idiopathic pleurisy is important supporting evidence as is also a familial suscepti-

tated into a dangerous crisis (3) Cutler Power and Wilder (1938) put the salt deprivation test on a more scientific and mathematical basis Thus

On the first day of the examination and thereafter until its close a diet low in salt was served which by calculation provided 0 95 gm of chlorid ion 0 59 gm of sodium and 4 1 gm of potassium The fluid intake of the first day was not measured but the free drinking of water was encouraged On the afternoon of the first day extra potassium was given as potassium citrate in a dose representing 33 mg of potassium per kilogram of body weight On the second day the intake of liquid was made to equal 40 c c for each kilogram of body weight and on the morning of this day the dose of potassium citrate was repeated On the third day 20 c c of liquid per kilogram of body weight was given before 11 a m At 12 noon of this third day the examination ended Blood was drawn in an oiled syringe from the cubital vein at 8 a m on the second day of examination and at 10 a m of the third day Urine was collected in three periods from 8 a m to 8 p m of the second day from 8 p m to 8 a m of the third day and from 8 a m to 12 noon of the third day

The results of the last period are the most important Immediately the test is ended cortical extract should be given to avoid a crisis The results were as follows the range of serum values for sodium and chlorine in Addison patients overlapped those obtained in normal controls and were not conclusive The sodium excretion on the third day however varied from 165 to 282 mg per 100 c c in Addison's disease compared with 6 to 85 mg per 100 c c in normal controls Similarly the chloride excretion was 229 to 365 mg per 100 c c compared with 17 to 141 mg per 100 c c in normal controls Dryerre (1939) confirmed these striking differences in sodium excretion of the patient with Addison's disease and of other individuals under the conditions of the Cutler test but found the chloride urinary values equivocal He confirmed that the serum values for sodium and chlorine were of no diagnostic value (4) *Kepler test* This test is remarkably reliable in my experience and has the advantage over the other tests in being without danger It is generally positive in Addison's disease and in other conditions where the adrenal cortex is not functioning e g Simmonds's disease It is negative in all conditions in which the adrenal gland is functioning normally with the exception of renal insufficiency This striking fact led me to undertake renal function tests in Addison's disease as well as the Kepler test I found that in a number of cases the two tests appeared to run

carcinoma the adrenals might themselves be affected or their sympathetic nerve supply be involved Pigmentation of the skin only however is not uncommon in any form of carcinoma Apart from disease although perhaps unnoticed until some illness is present pigmentation of the mucous membrane is found in persons in whose ancestry there is a strain of negroid Indian Eurasian or Levantine blood The racial factor is frequently forgotten or unknown but pigmentation may be found in other members of the family Pregnancy with vomiting in such a patient has in the writer's experience been wrongly diagnosed as Addison's disease Skin pigmentation however especially in brunettes is not uncommon in pregnancy and is explicable on the basis of the greater demand on adrenal function It also occurs with utero ovarian disorders and is termed chloasma

Pigmentation of the skin occurs in pellagra and a patient with pellagra secondary to gastro jejunostomy was sent to the writer with the diagnosis of Addison's disease other features being anorexia diarrhoea weakness anaemia and wasting The adrenals in fatal cases of pellagra however have been observed to be atrophic probably secondary to vitamin deficiency The skin in pellagra shows sharply demarcated areas of hyperkeratosis *Pigmentation of the skin is a rare complication* of exophthalmic goitre and it is not unlikely that in such cases the adrenals too are affected In fact it would not be too hazardous an hypothesis to suggest that in all cases of increase in the melanin pigment of the skin associated with disease there is a primary or secondary interference with the function of the adrenal cortex There is even less doubt of the truth of this hypothesis if we include pigmentation of the mucous membranes

(*b*) *Biochemical* (1) Low serum values for sodium and chlorine favour the diagnosis of Addison's disease but normal values do not exclude it This is also true of high serum potassium values high blood urea and non protein nitrogen and a low blood sugar (2) Harrop Weinstein Soffer and Trescher (1933) suggested and showed that a diet low in salt might be used as a diagnostic test in Addison's disease the clinical condition of the patient deteriorating markedly if the diagnosis was correct This was confirmed by Nettrour and Rynearson (1934) The test has the obvious disadvantage that the patient may thereby be precipi



Fig 44 (b)

(b) Pigmentation on mucous membranes inside the mouth



Fig 44 (a)

Fig 44 Addison's Disease In a woman of 39 showing (a) pigmentation on the face neck and arms

voided from 10 30 p m to 7 30 a m If the value of A in this equation is greater than 30 the patient probably does not have Addison's disease If the value for this equation is less than 25 the patient probably has Addison's disease provided that nephritis has been excluded

(c) *Therapeutic test* A patient with Addison's disease usually responds in dramatic fashion to adequate doses of cortical extract This test alone however is obviously not necessarily conclusive

(xx) Treatment

Prior to the preparation of potent extracts of suprarenal cortex the only systematic method of treating Addison's disease was that known as the Murhead regimen used at the Mayo Clinic in 1920 It was based on the use of adrenaline by subcutaneous oral and rectal routes and the giving of dried extract of suprarenal cortex by mouth A measure of success was obtained in some cases but the evaluation of more specific therapy showed the serious limitations and lack of scientific basis of this method of treatment

Hartman MacArthur and Hartman (1927) and Rogoff and Stewart (1928) prepared extracts of suprarenal cortex that were effective in maintaining adrenalectomized animals alive and had a measure of clinical success Swingle and Pfiffner (1929) however produced an extract which was more potent than previous preparations and which was successfully manufactured on a large scale and applied to the treatment of Addison's disease Rowntree and Greene (1931) were the first in America to report successful therapy with Swingle and Pfiffner's extract in that country and Simpson (1931) in England These reports were followed by a plethora of literature and the successful treatment of Addison's disease by adrenaline free cortical extracts was soon established on a sound basis

The next phase was the recognition of the importance of the adrenal gland in sodium metabolism and the value of common salt by mouth in alleviating symptoms and/or in permitting a reduction of the requisite dose of cortical extract (Loeb and colleagues 1935) Finally Reichstein and collaborators in Zurich (1936) and Kendall and collaborators at the Mayo Clinic (1936) working independently isolated several crystalline fractions from crude cortical extracts and synthesized them Of

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roughly parallel and if one looks at the formula of Kepler (1941) (see below) it is obvious that renal function plays an important part as well as the specific effect of the adrenal cortex, on mineral metabolism

Kepler test Procedure 1 On the day before the test the patient eats three ordinary meals but omits extra salt He is requested not to eat or drink anything after 6 o clock in the evening Until this time he may drink water as desired At 10 30 p m he is requested to empty his bladder and discard the urine All urine which is voided from then on until and including 7 30 a m is collected The volume of this urine is measured and saved for chemical analysis if this should be necessary later Breakfast is omitted The patient is asked to void again at 8 30 a m and immediately thereafter he is given 20 c c of water per kilogram of body weight (9 c c per pound) He is asked to drink this within the next forty five minutes At 9 30 10 30 11 30 a m and 12 30 p m he is requested to empty his bladder In order to eliminate the effects of exercise and posture on urinary excretion he is kept at rest in bed except when up to void Each specimen is kept in a separate container The volume of the largest one of these four specimens is measured

Under these conditions some patients having Addison s disease will *excrete so little urine that they are unable to void more than once or* twice during the entire morning In such instances the amount of urine excreted per hour may be calculated frequently however such calculations are unnecessary because of the very low urinary output throughout the entire morning

Inferences that may be drawn from Procedure 1 (1) If the volume of any single hourly specimen voided during the morning is greater than the volume of urine voided during the night the response to the test is negative that is such a response indicates the absence of Addison s disease (2) If the volume of the largest hourly specimen voided during the morning is less than the volume of urine voided during the night the response to the test is positive that is Addison s disease may or may not be present To establish the diagnosis procedure 2 should be *instituted*

Procedure 2 Blood is drawn while the patient is still fasting and the plasma analysed for its content of urea and chloride The specimen of urine which was voided during the night is also analysed for urea and chloride From these four determinations and from the results obtained from Procedure 1 the following equation is solved

$$A = \frac{\text{Urea in urine (mg per cent)}}{\text{Urea in plasma (mg per cent)}} \times \frac{\text{Chloride in plasma (mg per cent)}}{\text{Chloride in urine (mg per cent)}} \times \frac{\text{Volume of day urine (c c)}}{\text{Volume of night urine (c c)}}$$

The term day urine applies to the largest of the hourly specimens voided during the day night urine to the entire amount which was

voided from 10 30 p m to 7 30 a m If this value of A in this equation is greater than 30 the patient probably does not have Addison's disease If the value for this equation is less than 25 the patient probably has Addison's disease provided that nephritis has been excluded

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these desoxycortone has been used for some years with success in the treatment of Addison's disease (Simpson 1938 Thorn Howard and Emerson 1939) The acetate of desoxycortone was used as the esters of other hormones have been to prolong the duration of effect It soon became apparent that desoxycortone was not adequate therapy in all cases and that it was not the only essential constituent of a potent cortical extract (Simpson Himsworth 1939) Its action appears to be limited to its influence on salt and water metabolism and it does not remedy the disordered carbohydrate metabolism of adrenal insufficiency The latter is influenced by another group of hormones—corticosterone 11 dehydrocorticosterone and 11 dehydro 17 hydroxycorticosterone (compound E of Kendall) None of the members of this corticosterone group are as yet available on a large scale but they are contained in cortical extracts and at least one manufacturer assays their cortical extract for its influence on carbohydrate metabolism as well as on salt metabolism Nevertheless in some patients desoxycortone alone has had a high measure of success the assumption being that in these cases the adrenal insufficiency was only partial

(xxi) Technique of Therapy

(a) *Cortical extract* For convenience it is permissible to refer to cortical extract as cortin without however implying any particular extract It is given by intramuscular injection into the buttock or thighs The dose for a mild case is about 5 c c daily and for severe insufficiency 20 c c daily or more During period of infection or in the course of surgical procedures the quantity of cortin should be doubled or trebled When the daily dose is large cortin may be given twice daily If there is some pain on injection, 0 5 c c or less of 2 per cent novocaine may be added to the cortin in the syringe Persistent local reactions when cortin is given by the intramuscular route are unusual but one patient had such reactions even with 1 c c doses and these were sufficiently severe to prevent adequate therapy and death supervened This however, was somewhat exceptional *Cortin* may also be given intravenously and usually without any allergic reaction but apart from the technical difficulty of daily intravenous injections it has been shown that a refractory

state develops after some weeks (Hartman Lewis and Toby 1938) This does not occur with intramuscular injections Cortin is supplied in 10 c c rubber capped bottles and retains its potency for some months if kept in the cold Recently more potent extracts have been available and there has been considerable reduction in dosage

(b) *Desoxycortone acetate* (i) *Intramuscular injection* For this purpose desoxycortone acetate is prepared in ampoules of 1 c c of arachis or sesame oil containing 5 mg of desoxycortone acetate Judging by clinical experience Simpson (1938 1939) found that 5 mg was equivalent to 10 c c of cortin but Wilkinson (1939) thought that the equivalent in cortin was nearer 20 c c or even 30 c c Animal experiments (see Experimental section) indicate even greater relative potency of desoxycortone acetate As with cortin the beneficial effect is noticed within an hour and endures for some 12 to 24 hours Unfortunately in some patients severe local reactions occur at the site of injection and apart from its inconvenience the therapy by this route soon ceases to be effective in such cases I have also seen patients develop oedema after only 2 mg of desoxycortone daily although their adrenal insufficiency has not been relieved This however is quite unusual In many patients daily intramuscular injections of 5 mg desoxycortone may be quite effective therapy for years

(ii) *Cutaneous inunction* For this route 20 mg of desoxycortone acetate are dissolved in 1 c c ampoules of alcoholic solution (100 mg of benzyl alcohol) The contents of an ampoule are rubbed into the skin of the thigh or abdomen or arm by the patient the process taking some 10 to 20 minutes It is an easy and effective route of administration and quite painless The only disadvantage is the relatively high cost since the dose by this route is four times that by intramuscular injection Initial reports were made by the writer in 1939 and up to the present time this form of therapy has proved satisfactory in selected cases

(iii) *Insertion of tablets under the skin* In 1937 Deanesly and Parkes showed that oestrone and testosterone tablets inserted under the skin of animals were gradually absorbed over a period of months The writer in 1938 and 1939 used this technique for Addison's disease and published favourable

results (Simpson 1939) Initially, four tablets of 50 mg each of desoxycortone acetate were inserted in the subcutaneous fat of the abdomen under local anaesthesia This dosage proved sufficient for mild degrees of adrenal insufficiency but for more severe degrees 4 or 6 tablets of 100 mg each were employed The worst cases even with this dose required supplementary therapy with salt or injections of desoxycortone acetate Thorn and colleagues (1939) working independently used a similar technique in Addison's disease basing their dosage on animal experiments They suggested that for every 0 5 mg of hormone in oil required daily by the intramuscular route a tablet or pellet of 125 mg is required Thus for a patient requiring 5 mg daily by injection 10 or more tablets of 125 mg of desoxycortone acetate would be inserted under the skin In the writer's clinical experience this estimate is too high even after waiting several weeks for stabilization of the injected dose A ratio of 1 tablet of 100 mg or 125 mg for each 1 mg of injected material is advocated by the writer In any case from a practical point of view it is imprudent to exceed 400 mg as an initial implantation except in very severe cases owing to the risk of excessive water retention and it is advisable to have some weeks of injection therapy before implantation is carried out *The duration of effect appears to vary between 6 and 9 months* This individual clinical variation is at least partly due to the amount of hormone absorbed in the later months being *less than that in the earlier period and supplementary therapy* may be called for in the later months Thorn and colleagues (1939) found that the rate of absorption did not vary significantly in different animals and did not seem to be related to the animal's condition or hormone requirement Clinical evidence tends to confirm this and it is very important to remember that any extra requirements of hormone e g infection or special *exertion must be met by supplementary injections of hormone* preferably cortical extract or corticosterone compounds when available

(iv) *Dietary treatment* Wilder Kendall and collaborators (1937) found both adrenalectomized animals and patients with Addison's disease were sensitive to diets containing much potassium and that a crisis might thereby be precipitated They therefore planned low potassium diets containing 0 59 gm of



FIG 45 ADDISON S DISEASE Woman aged 7 Photograph illustrates dramatic appearance of leucodermia in Addison s disease This patient died in a hypoglycaemic crisis and autopsy revealed complete atrophy of both adrenal glands (One of Addison s own patients coming to autopsy had leucodermia)

sodium 0.91 gm of chloride and 1.6 gm of potassium, *per diem*. It was found that an intake of this quantity of potassium materially diminished the patient's requirement for salt and/or cortin; also that a daily intake of more than 4 gm of potassium significantly increased the urinary excretion of sodium chloride.

The assaying of a diet which will contain not more than 1.6 gm of potassium requires careful planning. Such a diet is likely to be inadequate in calcium, phosphate, iron, and vitamins *B* and *C*. To avoid complication from deficiencies of these factors the diet should be supplemented suitably by the addition of calcium phosphate, some iron salt, and a concentrate of vitamins B and G. Bearing these facts in mind, and the culinary difficulties, as well as the effect on the palate, the writer has found the disadvantages of such a diet outweigh the advantages and, where cortin or desoxycortine is available, few patients persist in the use of a low potassium diet. Further, a low potassium diet, if used in conjunction with desoxycortone, increases the liability to excessive water retention. Nevertheless, low potassium diets are included for those especially interested.

Low Potassium Diet (As used at the Mayo Clinic, Rochester, U.S.A., and planned by Sister Victor.)

Potassium 1.6 gm. Protein 57 gm. Calories 2,350

Food	*Grams*	*Approximate measure*
Breakfast		
Orange juice	100	½ glass
Cornflakes	15	1 serving
Egg	50	One
Bread	50	2 slices
Butter	20	2 squares
Cream, 40 per cent. fat	75	¼ of a cup
Coffee if desired		
Dinner		
Beef tenderloin (weight uncooked)	0	1 average serving
Potato, thrice boiled	100	1 average serving
Carrots	25	1 small serving
Celery	25	2 celery hearts
Grapefruit	55	4 sections
Bread	50	2 slices
Butter	25	2½ squares
Cream, 40 per cent. fat	20	1 tablespoon
Tea or coffee if desired		

Food	Grams	Approximate measure
Supper		
Cheese	40	2 cubic inches
Rice (weight dry)	[illegible]	1 average serving
Tomato	50	½ average serving
French dressing	15	1 tablespoon
Apple	80	½ average slice
Bread	50	2 slices
Butter	5	½ squares
Cream 40 per cent fat	20	1 tablespoon
Tea or coffee if desired		

This diet and indeed all the diets low in potassium that we have been able to plan contain what seems to be an adequate amount of protein but a bare minimum of calcium and other minerals The content of vitamins A and C is adequate but the content of vitamins B and G is low An important consideration therefore will be the matter of supplementing such diets with what is missing This can be accomplished by prescribing calcium phosphate an iron salt and a suitable concentrate of vitamins B and G

Directions for special cooking of vegetables

Vegetables like potatoes turnips and so forth should be peeled and cut into small thin pieces about ¾ inch square and ¼ inch thick Cabbage spinach and other leaf vegetables should be shredded Cauliflower should be broken into flowerets and the flowerets partially quartered that is split crosswise at the bud end Brussels sprouts likewise should be partially quartered String beans and asparagus should be cut into ½ inch pieces Peas are left whole For cooking use a deep narrow pan rather than one that is wide and shallow After being prepared the vegetables should be plunged into boiling salted water Use 1½ teaspoons of salt for each quart of water Cook gently as too vigorous boiling may cause the vegetable to break into pieces It is impossible to give the exact time for cooking any one vegetable The length of the cooking period will vary with each vegetable Test for tenderness by piercing with a fork After the vegetable is tender drain and gently heat over flame until dry

Season with salt and with butter cream or cream sauce

When cooking corn beets and tomatoes (either the raw cooked or canned product may be used) tie in moistened parchment paper immerse in boiling water and cook until tender Discard the cooking water The vegetable after being removed from the parchment paper bag should be seasoned with butter and salt and served hot

Directions for special cooking of meat

The less tender cuts of meat may be used for this purpose but the selection need not be limited to these Sear the meat cut into small pieces about ¼ inch square and ½ inch thick Transfer meat to a sheet of moistened parchment paper Tie paper with white string in the form

of a bag and immerse the bag in boiling salted water using the proportion of one part of meat and eight parts of water Example for ½ cup of cubed meat use 4 cups or one quart of water for each quart of water use two teaspoons of salt Simmer (cook just below the boiling point) for two hours The bag *containing the meat must* be kept under water during the entire cooking period Evaporation of water can be prevented to a large extent by using a covered pan but in case of evaporation the water should be replaced

At the end of two hours remove the bag from the water cut the string and empty contents into a convenient utensil The juice surrounding the meat should be used with it In meat and fish cooked according to this method the reduction of potassium averages 50 per cent

For special cooking of fish follow the directions given for meat Canned fish may be treated in the same way but need not be cooked longer than one hour

One or two drops of Worcestershire or A 1 sauce may be added to the meat before serving Larger amounts of meat sauce must not be used

(xxii) The Results of Therapy

(a) *Clinical* The initial results of the treatment of adrenal insufficiency *with cortical extract were dramatic and in a crisis* the effect was comparable to that of insulin in diabetic coma Nevertheless the clinical results over a long period were less satisfactory both as regards the failure of most patients to regain complete normality and the high death rate among patients treated over a long period Although the data on the latter point are somewhat inadequate a composite evaluation of published results and personal experience indicate that only 60 per cent of Addison patients survived for more than 5 years There is reason to believe that this is partly explained by the difficulties of producing on a large commercial scale cortical extract of sufficient concentration and potency Rowntree (1940) has recently recorded that six patients treated for 5 years with a cortical extract made by Professor Swingle in his laboratory remain alive and well in unusually good health and carrying on their jobs The writer found a similar extract kindly given him by Professor Swingle as long ago as 1930 more potent than any commercial *preparation he has since used and there* are indications that extracts of greater qualitative and quantitative potency may become more generally available

The isolation and synthesis of desoxycortone promised to solve the inherent difficulties of using a cortical extract of low

concentration and its introduction has proved of great practical value The failure however of some patients to respond adequately to desoxycortone acetate raised the possibility of this substance being only one of the essential hormones in a potent cortical extract (Simpson 1939) and this is now known to be the case The experimental finding that desoxycortone has little or no influence on carbohydrate metabolism as compared with corticosterone suggested that both these substances may be necessary Since however the writer has recorded (1932) good clinical results with cortical extract in spite of a persistently low blood sugar of 60 to 65 mg there may be a further factor involved and an amorphous fraction has been shown to have a very potent life saving effect in adrenalectomized animals (see Physiology section) From a practical point of view it can be concluded that when a patient is not doing well on what should be an adequate dose of desoxycortone acetate supplementary therapy with cortical extract is indicated If a patient on desoxycortone therapy suddenly collapses or behaves queerly hypoglycaemia should be suspected

Where injections of desoxycortone are irksome or produce local reactions the method of inunction or of subcutaneous insertion of tablets of desoxycortone should be employed Both cortical extract and desoxycortone acetate ameliorate or in many cases abolish the symptoms of Addison's disease Ferrebee and colleagues (1939) state of desoxycortone that clinically there is unequivocal improvement far greater than has resulted from any therapy hitherto advocated Wilkinson (1939) found that using either the natural or the synthetic cortical hormone the asthenia muscular weakness nausea and vomiting are rapidly relieved appetite returns weight increases and the pigmentation becomes less marked With cortical extract there is a tendency for a low blood pressure to gradually return to normal levels but chronic hypotension may persist in spite of excellent clinical improvement This is rarely the case with desoxycortone and the latter may even produce hypertension

Crisis In addition to the use of cortical extract or desoxycortone it was usually thought necessary to counteract severe dehydration by intravenous saline This sometimes has the disadvantage of producing rigors or other allergic manifestations which may prove fatal Since much of the fluid has passed into

the muscles and liver cortin or desoxycortone alone will produce a redistribution of such fluid In practice the writer rarely finds

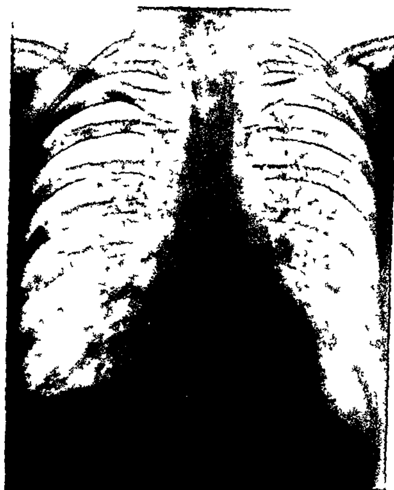


Fig 46 (a)

Fig 46 X ray photographs illustrating the effect of over dosage with desoxycortone (a) retention of fluid in the lower half of both lungs manifested clinically only by a few crepitations

it necessary to give intravenous fluid Twenty cubic centimetres of cortin or 10 mg of desoxycortone acetate are injected 4 hourly by the intramuscular route until the patient has recovered from the acute phase Most patients respond to such

treatment without any intravenous therapy The latter however should not be withheld if the collapse is extreme It is safer

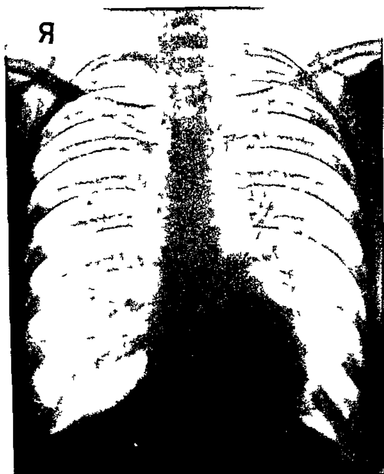


Fig 46 (b)

(b) Normal lungs after withdrawal of desoxycortone for three days The technique in radiography (Dr E Rohan Williams) and printing was identical in both (a) and (b)

to supplement desoxycortone with cortical extract in a crisis and the latter is called for on the experimental evidence Nevertheless I can record two patients in crisis treated successfully with desoxycortone only If hypoglycaemia is the more

immediate cause of the crisis or a complication of crisis cortical extract and intravenous glucose are indicated

Overdosage Desoxycortone is a very powerful hormone and the dangers of overdosage are considerable Clinically there result hypertension oedema of the subcutaneous tissues and of the lungs ascites and pleural effusion cardiac dilation and failure Such effects are more likely to occur when salt is given as additional therapy and this therefore should be done with the greatest caution and discrimination Unfortunately fluid retention may involve the lungs and pleura without any superficial oedema and without hypertension It may be detected by crepitations heard at the base of either lung and can be corrected by giving potassium salts and by mercurial diuretics Further excessive retention of fluid can occur with serum sodium and chloride concentrations within normal limits The serum potassium however is lowered and this is the best chemical indication of an excessive dose of desoxycortone This effect on potassium is in my opinion specific and is associated with severe myasthenia In one case under my care the serum potassium was lowered by intensive treatment with desoxycortone from 24 mg to 13 mg per 100 c c without the serum sodium and chloride being raised above normal The daily dose of desoxycortone should never exceed 5 mg unless adequate biochemical controls are available and it is safer to keep an initial implantation of desoxycortone at or below 400 mg unless a daily injection of 10 mg of desoxycortone has been proved to have no adverse clinical or biochemical effects Several observers (Ryan and McCullogh 1940 Simpson 1944) have reported the adverse effects of overdosage with desoxycortone but it is not realized that similar effects of water retention and lowered potassium concentrations in the serum can be obtained with cortical extracts providing that sufficiently large doses have been given This is very important as it is generally stated that cortical extract can be given in unlimited quantities without there being any danger of overdosage This statement is untrue although with moderate dosage i e less than 20 c c daily one is unlikely to obtain excessive water retention with cortical extracts

(b) *Chemical* Wilkinson (1939) found that both cortical extract and desoxycortone cause the blood chemistry to return

to normal Most observers agree that this is a tendency but that normal values for serum sodium and chlorine may fail to be attained with cortical extract even in the presence of a good clinical condition (Allott 1936) With desoxycortone acetate on the other hand there nearly always result a marked retention of sodium and chlorine a positive sodium and chloride balance and a restoration of plasma concentration of sodium and chloride to normal (Thorn Howard and Emerson 1939) These values may even be restored to normal when the clinical condition still leaves much to be desired (Simpson 1939) as might well be expected from more recent knowledge of the corticosterone group of substances A raised serum potassium returns to normal with desoxycortone and may be depressed considerably below normal concentrations with grave consequences The writer has suggested that this effect on potassium is specific and not merely secondary to the effect on sodium

Blood urea returns from raised to normal values with desoxycortone or cortical extract If fasting blood sugar values are low in the untreated state they may remain low under desoxycortone therapy and hypoglycaemic attacks may occur and even be fatal Cortical extract or corticosterone tends to raise blood sugar values to normal

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CHAPTER XVIII

HYPERADRENALISM

Phaeochromocytoma of Adrenal Medulla

Introduction

ADRENALINE SECRETING tumours of the adrenal medulla are comparatively rare and in the past have often eluded diagnosis before autopsy The first complete study of a classical case was made in 1922 by Labbe Tinel and Doumer and since that time more than a hundred cases have been recorded The disease may occur at all ages including childhood and the sex incidence is about equal The disease has been recognized more frequently clinically in the second and third decades of life (Howard and Barker 1937)

(*a*) *Pathology*

Phaeochromocytoma differ essentially from non endocrine tumours of the adrenal medulla namely sympathoblastomas and ganglioneuromas in that the cells secrete adrenaline and have an affinity for chromic acid Most of these tumours are also found to contain a great excess of adrenaline e g 280 mg compared with the normal content of 6 mg Phaeochromocytomas are also called paragangliomas but the latter term should be dropped as it may be confused with non endocrine ganglioneuromas Adrenaline in the cytoplasm of the cells of the phaeochromocytomas reduces chromium salts to form an insoluble peroxide of chromium which appears in the cytoplasm as fine brown granules

The tumours vary enormously in size from that of a pea to a grape fruit tumours weighing up to 2 000 gm having been recorded (Kirschbaum and Balkin 1942) The tumours are encapsulated and rounded and frequently show cystic degeneration of their otherwise solid homogeneous light brownish cut surface The moderate cellularity the relatively large polyhedral cells with extreme anisocytosis and poikilocytosis in some areas and an atypical arrangement of cells in others are characteristic In contrast with tumours of the cortex there is

an absence of fat lipoid and glycogen (Wells and Borman 1937)

Although in the recorded operated cases the tumour has been *found twice as frequently on the right than the left Brunschwig* and Humphreys (1940) state that of 103 reports (mostly of necropsies) 43 concerned the right and 34 the left adrenal there were 13 instances of tumours in each adrenal and in 13 instances the neoplasms were entirely outside the adrenal glands McGavack et al (1942) record eight cases of malignant phaeo chromocytomas from the literature including one patient under their care No less than five of these eight cases were bilateral Multiple metastases occurred

(b) Clinical

The symptoms are due to the paroxysmal discharge of large quantities of adrenaline into the circulation and in some cases there is a continuous secretion of adrenaline in abnormal quanti ties as well as superimposed exacerbations Attacks may occur at intervals of weeks or several times a day and may last from a few minutes to a few hours In an attack the patient may experience anxiety palpitations tremors perspiration severe headache blurred vision faintness weakness dyspnoea a feel ing of suffocation or painful constriction of the chest or angina like pain nausea vomiting abdominal colic cramps of the calf muscles and tingling of the extremities which may undergo colour changes comparable to those found in Raynaud s disease The blood pressure may be normal in quiescent periods and suddenly rise in attacks or it may be appreciably raised chronically and rise still farther in paroxysms The pulse rate is considerably accelerated during attacks The systolic pressure is said to rise to a greater extent than the diastolic but both may be raised considerably e g 280 systolic and 200 diastolic The heart may be considerably enlarged and left ventricular failure ensue Pulmonary oedema with frothy blood tinged sputum is also met with In one case (Goldsenhoven and Vandenbroucke 1945) phases of hypertension *(240/150 mm)* were followed by phases of hypotension (90/70 mm) The clinical picture may be one of severe progressive hypertension e g 200/110 mm without any superimposed paroxysms as in the woman of *29 years of age described by Binger and Craig*

(1938) The fundi may show papilloedema or hypertensive retinitis and these changes may be reversible if the tumour is removed early enough The kidneys may or may not be secondarily involved but nephrosclerosis has been recorded (Green 1946) In most cases the urea clearance test of kidney function gives values well above normal e g 140 per cent and this is attributed to the increased blood flow through the kidneys

The basal metabolic rate is often raised to the extent found in hyperthyroidism e g plus 60 per cent but this is not due to hyperthyroidism since it disappears after removal of the adrenal tumour and was unaffected by removal of an enlarged thyroid gland in the relatively few cases in which the latter has been present The structure of the thyroid gland is not hyperplasia as in thyrotoxicosis but that of a colloid goitre or colloid adenoma An apparently normal thyroid gland may become enlarged and vascular during an attack The increased basal metabolic rate is often associated with pyrexia which may be constant or intermittent Some upper lid retraction or apparent exophthalmos may be present but is usually variable as is the associated mydriasis

Diabetes mellitus has often been diagnosed as a complication but here too the hyperglycaemia is a result of the hyperadrenalism The blood sugar concentration is variable and unstable and the patient hypersensitive to insulin McCullagh and Engel (1942) recorded the following blood sugar tolerance curves before and after removal of an adrenal phaeochromocytoma the values being fasting and at 30 minute intervals after 100 gm glucose

Before	1 8	267	254	75	45	76	mg per 100 c c
After	88	168	168	108	49	72	mg per 100 c c

Although phaeochromocytomas are limited to the adrenal medulla in very rare instances the cortex may be functionally involved either in the direction of hypercorticalism or hypocorticalism Thus Neff and colleagues (1942) described an instance in a girl of 16 months in which in addition to the hyperadrenalism hirsutism acne and hypertrophy of the clitoris were present and disappeared after removal of a phaeochromocytoma which did not encroach upon the cortex as seen

histologically Signs of hypocorticalism described by McGavack and colleagues (1942) as those of Addison s disease are exceptionally met with in unilateral benign or malignant phaeochromocytoma without apparent involvement of the cortex

McGavack (1942) collected eight cases of malignant phaeochromocytoma the average age being 45 years and the youngest 13 and he emphasizes the absence of bouts of paroxysmal hypertension and other manifestations of hyperadrenalism Multiple metastases were common and the clinical features those of cachexia and pain In no less than five of the eight patients the malignant phaeochromocytomas were bilateral In a review of the literature however I find two cases of malignant phaeochromocytomas with hypertensive paroxysms and the same clinical features as those of non malignant phaeochromocytoma one in a girl of 14 (Ernould and Picard 1934) and the other in a woman of 44 who died in a hypertensive crisis (Goidsenhoven and Vandenbroucke 1945) In the latter instance however there were no metastases and the diagnosis was made on histological grounds by the pathologist In the case of the girl of 14 there were multiple metases and cachexia It can be concluded therefore that malignant phaeochromocytomas may give rise to symptoms of hyperadrenalism but more usually these symtoms are absent

(c) *Diagnosis*

Paroxysms of hypertension and tachycardia with pallor perspiration and apprehension are characteristic and the intervening periods may show a normal or a raised blood pressure Manual pressure in the loins may occasionally produce an attack Roth and Kvale (1945) demonstrated that 0 025 mg of histamine injected intravenously produced a typical attack in a patient with phaeochromocytoma the mechanism being release of adrenaline A similar attack could be induced by the cold pressor test immersing the extremities in cold water A diabetic type of tolerance curve and raised basal metabolism would favour the diagnosis The latter is uninfluenced by iodine or thiouracil Intravenous pyelogram may show a depression of the renal pelvis on the same side as the tumour, but a negative finding is not significant A pressor substance with an adrenaline like action (perfusion of the denervated ear of a rabbit) may be

found in the blood during paroxysms (Beer King and Prinzmetal, 1937)

(*d*) *Treatment*

This consists of removal of the tumour The approach may either be anterior abdominal or posterior retro peritoneal Manipulation at operation may indicate the site of the tumour if it is not definitely known by producing a rise of blood pressure and pulse rate Removal of the tumour may be followed by a severe fall of blood pressure and collapse Intra venous saline and injections of adrenaline and desoxycortone should be available in anticipation In one case in which a portion of tumour was left behind clinical relapse reponded to deep radiation on two occasions (Goid enhoven and Vandenbroucke) but such treatment is usually ineffective as a primary treatment

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SECTION THREE

THE THYROID

A PHYSIOLOGY

CHAPTER XIX

INTRODUCTION

THE physiology and biochemistry of the thyroid gland is relatively simple compared with the other endocrine glands in so far as it secretes one hormone thyroxine and its prepotent function through this hormone is the regulation of the metabolic rate There are other less direct effects on gonads lactation and growth We have seen in the Pituitary section that hypophysectomy leads to involution of the thyroid and conversely the pituitary thyrotrophic hormone produces hyperplasia and hyperfunction of the thyroid gland The function of the thyroid gland is dependent upon a proper supply of iodine which is an essential constituent of thyroxine Certain goitrogenic substances prevent the synthesis of thyroxine even in the presence of a plentiful supply of iodine

HISTOLOGY

The resting or normal structure of the gland consists of vesicles which contain colloid and are lined by a single layer of low cuboidal or flattened epithelium The hyperplastic structure consists of vesicles containing little or no colloid and lined by high columnar epithelium plicated and duplicated with the cells showing active mitotic division Though hyperplasia is often associated with hyperthyroidism it indicates hyperactivity but not necessarily hyperfunction Hyperplasia may indicate an endeavour of the gland in the presence of a deficiency (relative or absolute) of iodine to produce the normal thyroxine requirements But such hyperactivity may *still not equal the* efficiency of the normal working gland In fact hyperplasia may be accompanied either by hypothyroidism or by hyperthyroidism or by any intermediate stage

Adenomas (αδηυ a gland) are new formations of epithelial gland tissue which resemble the glandular tissue of the organs in which the tumours arise Adenomas may be single or multiple in the latter ca e being regarded as expressions of hyperactivity (not necessarily hyperfunction) of the whole gland but when single as of embryological origin—foetal cell rests

THYROIDECTOMY

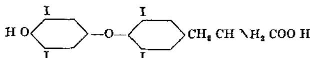
The effect of the operation depends upon the age of the animal the most striking effect in immature animals being the severe retardation of growth (comparable to that in cretinism) What ever the age there is a decrease in metabolism and body tem perature and an increased sensitivity to cold loss of muscle tone weakness anaemia dryness and lo s of hair an increase in carbohydrate metabolism and a disturbance of gonadal func tion and of pregnancy Chu (1944) has shown that in the rabbit thyroidectomy produces an increase of follicle stimulating hor mone but a disappearance of ovulating and luteinizing hor mone so that ovulation does not occur after coitus in the thyroidectomized animals The pituitaries of thyroidectomized animals contain little or no ovulatory hormone but large amounts of follicle stimulating hormone Further the thyroid hormone is necessary for the maintenance of the vitality and growth of the embryo durin_ gestation In early pregnancy in the absence of the thyroid gland death and resorption of the embryo takes place and in the late stages abortion with still birth of the majority of the embryos Prolongation of gestation owing to retention of dead foetuses may occur All these effects may be prevented by feeding thyroid gland The giving of thyroid extract to normal intact rabbits produced complete inhibition of ovarian activity

Thyroidectomy produces also histological changes in the anterior pituitary gland namely a disappearance of eosinophil cells and an increase in chromophobe and basophil cells The latter are vacuolated but can be distinguished by their Golgi apparatus from basophil castration cells

THYROXINE

The thyroid gland secretes only one hormone namely thy roxine which substance is a combination of iodine with an organic nucleus Oswald (1899) first prepared such a substance

iodothyreoglobulin whose activity corresponds to that of the dried thyroid gland (thyroideum) Kendall (1915) hydrolized a thyroid protein and obtained an indole derivative which he called thyroxine Harrington (1926) carried the analysis a step farther and showed that thyroxine was not an indole derivative but the *p* oxy diiodophenyl ether of the amino acid tyrosine $C_{15}H_{11}O_4NI_4$ and he was able to synthesize thyroxine



The normal thyroid gland secretes approximately 1 mg of thyroxine daily Thyroxine is stored in the colloid portion of *the thyroid gland so that colloid adenomatous goitres contain* a large amount of thyroxine whereas the hyperplastic gland found in primary thyrotoxicosis contains relatively little thyroxine However the activity of the gland determines the concentration of organic iodine in the blood and this is high in thyrotoxicosis and low after thyroidectomy or in myxoedema

Thyroxine and dried thyroid gland are active when taken by mouth It is also interesting to note that when a single intravenous injection of thyroxine is given there is a latent period of 48 hours before its activity is manifested metabolically and the action continues for some 3 weeks No satisfactory explanation of this latent period or of the long duration of action has been made

The chief action of thyroxine is to accelerate metabolism especially the process of oxidation and the usual method of measuring the degree of thyroid activity is by estimation of the basal metabolic rate i e the amount of oxygen used by the patient in a given time while at rest under standardized conditions In thyrotoxicosis this increased rate of metabolism is *inadequately compensated for by increased appetite and* food intake so that the patient loses weight Apparently the metabolism of carbohydrate protein and fat are all involved The former is indicated by depletion of hepatic glycogen glycosuria hyperglycaemia and occasionally by diabetes indistinguishable from pancreatic diabetes the breakdown of muscle protein is evidenced by creatinuria and fat catabolism by a fall in blood lipase and the diminution of fatty tissue Nevertheless thyroid

therapy is inadequate in pituitary adiposity its toxic effects being manifested before appreciable influence on fatty tissue can be observed and further severe myxoedema may be met with in the absence of adiposity Ketosis is rare in thyrotoxicosis

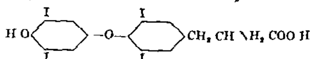
Thyroxine also produces an acceleration of the heart metamorphosis of the tadpole gastro-enteritis and diarrhoea an increased excretion of calcium particularly in the faeces erythropoeisis diuresis and enlargement of some organs e g liver kidney heart and adrenals Dried thyroid gland given experimentally to rats produces similar results and depression of sex function

IODINE AND THYROID FUNCTION

Iodine is an essential constituent of the thyroid hormone thyroxine and the adequacy or inadequacy of its supply to the organism influences thyroid function Thus a deficient supply of iodine leads to hyperplasia of the vesicular epithelium in an attempt to maintain a normal synthesis and secretion of thyroxine an attempt which cannot succeed because an essential constituent of thyroxine namely iodine is deficient or absent The hyperplasia may be followed by exhaustion of cellular activity and atrophy or by a return to a resting phase (Marine) Such a deficiency of iodine in the water supply or food is believed to be the cause of endemic goitre which can be largely prevented by minute quantities of iodine in table salt or sweets

The quantity of iodine necessary for normal metabolism is however remarkably small Thus to keep a normal person in iodine balance an intake of 100 to 200 micrograms of iodine in 24 hours is sufficient (a microgram is one thousandth part of a milligram and is sometimes designated μ) The human body as a whole contains approximately 40 mg of iodine which is widely distributed throughout the organism including the muscles but one fifth of the total iodine is present in the normal thyroid gland which weighs about 20 gm It is interesting to note that 1 minim of Lugol s iodine contains 6 mg of iodine approximately as much as is present in the normal thyroid gland In terms of thyroxine the human thyroid usually secretes about 1 mg of thyroxine daily and thyroxine contains 65 per cent iodine Salter found that not more than 10 per cent of the total iodine in the thyroid gland was inorganic in nature 90

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per cent or more was in organic combination (thyroglobulin) approximately two thirds of this being in the form of diiodo tyrosine and one third thyroxine Diiodotyrosine has no thyroxine like action *A deficiency of tyrosine as well as a deficiency of iodine* can prevent the synthesis of thyroxine

The total blood iodine in normal subjects varies between 4 and 8 micrograms per 100 c c but its level is not necessarily an *indication of the* degree of thyrotoxicosis and it may be raised in normal people especially when they have received iodine or iodides The level of protein bound iodine however does appear to be a good indication of the degree of thyrotoxicosis (high values e g 8 to 16 mg per 100 c c) or of myxoedema (low values e g 2 micrograms per 100 c c compared with a normal of 4 to 6 micrograms) Some observers consider that the concentration of protein bound iodine in the blood is a better measurement of thyroid function than the basal metabolic rate or the blood cholesterol (the latter tends to be low in thyrotoxicosis and high in myxoedema) Organic iodine in the blood is associated almost *entirely with the albumen fraction* as *distinct from the globulin* fraction Protein bound iodine is estimated after precipitation of the protein and the free iodine value is the difference between total iodine and protein bound iodine In normal subjects not taking iodine the protein bound iodine constitutes 70 per cent of the total iodine and the free iodine 30 per cent Apart from the fact that different chemical methods produce slightly different proportions of protein bound and free iodine the giving of iodine in medicines or food increases the free iodine and total iodine without affecting the protein bound iodine Except in certain laboratories the estimation of blood iodine has not become a popular procedure among clinicians

THYROTROPHIC HORMONE

In the Pituitary section it has been pointed out that among other effects hypophysectomy leads to rapid involution of the thyroid and a fall in basal metabolism e g —40 per cent The epithelium of the thyroid vesicles becomes flattened and the intravesicular colloid stains poorly These observations indicated that the activity of the thyroid gland was stimulated by a pituitary hormone called thyrotrophic hormone and a chemical extract of the pituitary gland has been prepared

which when tested on hypophysectomized animals produces a return of thyroid function and structure to normality or to hyperactivity In normal animals such preparations of thyrotrophic hormones produce within 18 hours a hypersecretion of thyroxine and an increase of basal metabolism e g +80 per cent The cuboidal cells lining the vesicles become columnar and undergo hypertrophy and hyperplasia the multiplying and actively dividing cells forming several layers with intravesicular plications giving the appearance of a lace network The colloid disappears The appearance of the gland is comparable to that found in primary thyrotoxicosis

After some 10 days of injections of a thyrotrophic preparation the animal becomes refractory to them and there is a reversion to normal thyroid function and structure or transient slight subnormality This is apparently due to the formation of antibodies within the injected organism and serum from such an animal when injected into a normal animal can prevent thyrotrophic hormone from having any effect It is believed that these antibodies are specific for certain species e g pig or cattle pituitary preparations but not for all thyrotrophic hormones whatever their source and that they are chemical antibodies produced by injected foreign proteins probably associated with the thyrotrophic hormone rather than identical with it

If iodine is given at the same time as thyrotrophic hormone is injected its effect will be prevented or minimized since the thyroxin that is formed by increased activity of the thyroid gland will be stored in the intravesicular colloid and not allowed to enter the blood stream

The essential activity of the thyrotrophic hormone as presented above and its mode of action indicate that it would be ineffective in thyroidectomized animals and this is found to be the case Nevertheless it still produces one effect even in the absence of the thyroid gland and that is the production of exophthalmos The exact mechanism is not understood but the experimental finding is important as an explanation of why exophthalmos may persist or even become aggravated after a thyroidectomy for thyrotoxicosis and when the basal metabolism has been reduced to normal or subnormal

Scowen (1937) has shown that the human thyroid in normal man reacts to thyrotrophic hormone exactly the same as that of

the rat or guinea pig and that after 10 days a refractory period sets in These observations are also true of the involuted thyroid of surgically hypophysectomized man or of hypothyroidism secondary to hypopituitarism but in myxoedema a primary thyroid disorder thyrotrophic hormone has no such effect

GOITROGENIC AGENTS

This term is used to indicate any substance which produces an enlargement of the thyroid gland irrespective of its histology as the latter varies with the phase and conditions of the experiment David Marine of the Montifiore Hospital New York has carried out with his colleagues over a number of years much fundamental experimental work on goitrogenic agents and Spence and Scowen in this country have added materially to our knowledge by their experiments Chatin as long ago as 1850 showed that in the regions of endemic goitre in the Alps the soil water and foodstuffs grown in those parts have a low iodine content This has been confirmed and reproduced experimentally and further very small doses of iodine have greatly reduced the incidence of goitre in such areas Marine has shown that the initial change in the thyroid is hyperplasia of the lining cells of the vesicles, followed by exhaustion atrophy or if iodine is given by a return to a colloid resting phase and ultimate normality This is called the thyroid cycle which can be produced repeatedly by variation in iodine supply and which is believed to take place in man However iodine is not the only factor McCarrison in India failed to confirm an iodine deficiency in endemic goitre areas but observed a general vitamin deficiency Experimentally a vitamin deficient diet involving A B C and D or any of these separately can produce a goitre with similar histological phases to those found with iodine deficiency Nevertheless vitamins do not prevent an iodine deficiency goitre developing and to a less extent the opposite is true

Cyanides

Marine found that the feeding of cabbage could produce a goitre in rabbits the thyroid becoming *three times the normal* size Iodine could prevent this or if given subsequently could produce a return of the hyperplasia to a resting colloid phase

The development of goitre could also be prevented by the feeding of certain fresh plants lawn grass fresh alfalfa hay and the pressed juice of steamed cabbage All these were found to contain large amounts of a reducing substance which could roughly be measured by its capacity to absorb iodine Contrary to expectation this substance did not prove to be vitamin C which has no anti goitrogenic action and its identity is still unknown

All of the goitrogenic cabbage family contain organic cyanides which are powerful depressors of oxidation It was found that methyl cyanide is as effective as cabbage in producing goitre and that it probably acts by reducing tissue oxidation to which the thyroid responds by attempting to produce more thyroxine but without success The latter view is confirmed by the fact that thyroxine or dried thyroid will stop a goitre developing and further that the goitre response to cabbage may be associated with hypothyroidism Inorganic cyanide although not so effective in the small experimental animal has been found to produce goitre associated with myxoedema in man incidental to the treatment of hypertension by thiocyanates (Rawson and colleagues 1943) It only occurs in a small percentage of patients and there is a return to normal thyroid function on cessation of the thiocyanate therapy A possible clue to the hormone action of thiocyanate was the production of exophthalmos in treated animals and its persistence after thyroidectomy which suggested that it might act by the mechanism of increased secretion of pituitary thyrotrophic hormone This has now been conclusively proved for goitrogenic cabbage (or rape seed) is ineffective in hypophysectomized rabbits and when it is effective in normal rabbits produces enlargement of the anterior pituitary gland increase in the number and size of the basophil cells as well as hyalinization and vacuolization of these cells (Kennedy and Purves 1941 and Griesbach 1941) Such changes in the pituitary are prevented or reversed by iodine or thyroxine Exophthalmos both experimentally and in man can occur in the presence of hypothyroidism as well as hyperthyroidism its production being dependent upon the secretion of pituitary thyrotrophic hormone

We have seen in a previous section that the influence of the pituitary on thyroid activity has been known for many years

(Houssay) and that Collip and his collaborators prepared a pituitary thyrotrophic preparation free from adrenocortico trophic hormone Therefore its action has nothing to do with the adrenal gland Apart from this however Marine has pointed out that sublethal injury of the suprarenal cortex in the cat or rabbit produces thyroid and thymus hyperplasia and an increased basal metabolism for weeks or months Further a striking involution of the adrenal cortex occurs in infants after the eighth day of life and goes on for the next 4 weeks to the accompaniment of a rapid increase of metabolism and heat pro duction Rats treated with goitrogenic cabbage show hyper trophy of the adrenal cortex as well as of the thyroid

Thiouracil

In 1941 C G and Julia MacKenzie opened up a new field by discovering that sulphaguanadine used by them to combat intestinal infections in rats turned out to be a powerful goitro genic agent the rat thyroid becoming 4 to 8 times its normal size in a few weeks The glands were hyperaemic and hyper plastic the vesicular epithelium becoming columnar and pli cated and the colloid disintegrating and disappearing At the same time however the basal metabolism fell to minus 20 per cent so that the sulphaguanadine produced a histological picture of hyperthyroidism but a metabolic hypothyroidism There were coincident changes in the anterior pituitary gland namely a decrease in eosinophil cells and an increase in basophil cells with degranulization and vacuolization of the latter sug gesting that the thyroid hyperplasia was attained through secre tion of pituitary thyrotrophic hormone This was confirmed by the ineffectiveness of sulphaguanadine in hypophysectomized rats All effects were prevented by the simultaneous administra tion of thyroxine but unlike cabbage goitre iodine did not prevent them It was postulated that sulphaguanadine acts by preventing the synthesis of thyroxine by the thyroid gland Kennedy and Purves (1941) carried things a step forward by isolating allyl thiourea from goitrogenic rape seed and showing that its action was identical with that of sulphaguanadine It also produced pulmonary oedema in rats Thiouracil has a similar action to thiourea and their inhibition of thyroxine formation is shown by the prevention of metamorphosis in tad

poles and the production of cretinism in young rats If any colloid is present in thiourea treated rats it is very low in iodine content and when iodine is given to such rats only a fraction is taken up by the thyroid gland

CARBOHYDRATE METABOLISM IN THYROTOXICOSIS

W T Anderson wrote a classical paper on this subject in 1931 and the facts apart from the theories hold good to day The majority of patients with thyrotoxicosis show a trace or more of sugar in the urine if the latter is examined frequently enough over a long enough period and some show intermittent glycosuria every day The fasting blood sugar is nearly always normal but in the few in which it is raised this is rarely above 130 mg per cent unless clinical diabetes is a complication In the majority of cases the carbohydrate tolerance curve (oral route) shows a rise above normal limits (e g 200 or 220 mg compared with 160 mg per 100 c c) and the fall of blood sugar concentration to normal values is delayed beyond 2 hours In some cases there is a rapid rise of blood sugar concentration above normal but a rapid fall to normal levels (lag curve) In other cases the carbohydrate tolerance curve is quite normal The renal threshold for sugar is not infrequently slightly below normal but diabetes innocens or renal glycosuria is a rarity In some 2 per cent of cases true diabetes mellitus occurs Anderson does not discuss the differentiation between diabetes mellitus as a complication of thyrotoxicosis and the latter disorder associated with carbohydrate tolerance curves of diabetic type as described above The blood sugar curves do not always permit an absolute differentiation from milder forms of diabetes mellitus and the latter diagnosis must therefore be based upon associated clinical features of this disorder Wilder of the Mayo Clinic (1940) points out that in hyperthyroidism the respiratory quotient rises more abruptly than normal after glucose (indicating oxidation of glucose at a normal or supernormal rate) whereas in diabetes mellitus the rise in the respiratory quotient after glucose is usually sluggish and in cases of severe diabetes no response at all is obtained

Adequate thyroidectomy abolishes the abnormal carbohydrate tolerance curves and the intermittent glycosuria in thyrotoxicosis unless clinical diabetes is present In the latter

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threshold for galactose is absent or very low Blood galactose may be estimated by the Hagedorn–Jensen or Folin–Wu method after the glucose in the blood is fermented by the addition of a yeast suspension The maximum blood concentration occurs at the end of the first hour after the ingestion of 40 gm galactose in 400 c c cold water and in normal control subjects is 20 to 30 mg per 100 c c In thyrotoxic patients it is above 50 mg and in severe cases of thyrotoxicosis above 200 mg per 100 c c The galactose index G I is the sum of the blood galactose values in mg per 100 c c at ½ 1 1½ and 2 hours In normal controls it is under 100 whereas in thyrotoxic patients it is rarely below 120 and usually over 200

The intravenous galactose test however shows no difference between normal and thyrotoxic patients and this indicates that the increased galactose blood concentration in thyrotoxicosis by the oral test is due to more rapid absorption of galactose from the gastro intestinal tract in thyrotoxicosis The normal blood galactose values after intravenous galactose also excludes the alternative theory of liver damage being the cause of the oral galactose tests Liver damage does occur in thyrotoxicosis and is revealed by more sensitive tests e g hippuric or bromsulph thalein tests and when severe enough even by the intravenous galactose test

The oral galactose tolerance test is considered by some observers to be more reliable than the basal metabolic rate in the diagnosis of thyrotoxicosis and of its severity

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case it is said to lessen the severity of the diabetes and the insulin requirements but in my experience this is by no means the rule Wilder and colleagues (1934) performed total thyroidectomy in a patient with severe diabetes mellitus without any thyrotoxicosis and found that although the patient s tolerance *was greatly improved the remedial result was not sufficient to justify recommending the procedure as a treatment for diabetes* Thyroid extract by mouth appears to exacerbate the severity of pancreatic diabetes mellitus

There are several factors contributing to the abnormal blood sugar tolerance curves in thyrotoxicosis The comparison of oral and intravenous routes shows that there is an increased rate of absorption of glucose from the gastro intestinal tract and this may account for the sudden rise and sudden fall type of curve This is only one aspect however for Wilder and Sansum found that whereas normal control subjects will accept continuous injections of dextrose at a rate of 0 8 gm per kilogram of body weight without passing sugar in the urine patients with thyrotoxicosis excrete sugar when the rate of injection is only 0 6 gm or less per kilogram per hour Thyroid feeding to experimental animals (rats cats) prevents the hepatic formation of glycogen and accelerates glucose formation from hepatic glycogen whereas thyroidectomy diminishes the hyperglycaemic reaction to adrenaline The livers of thyroid fed animals contain no glycogen unless high carbohydrate feeding has been possible and then only small amounts of glycogen

Glasser (1926 quoted by Wilder) noted hydropic degeneration and atrophy in the pancreatic islands of mice after continued injection of thyroxine and Holst (1932) observed degenerative lesions in the islets of Langerhans in patients dying from thyrotoxicosis *It would therefore appear that continued* hyperglycaemia in thyrotoxicosis as in pituitary hyperglycaemia (see Pituitary section) may produce islet cell degeneration in the pancreas and a secondary pancreatic diabetes but this occurs only in a small percentage of thyrotoxic patients

(a) Galactose Tolerance Tests in Thyrotoxicosis

When galactose is taken by mouth it is absorbed into the blood stream and converted into glycogen by the liver but the liver glycogen is not reconverted into galactose The renal

B CLINICAL

HYPERTHYROIDISM

CHAPTER XX

THYROTOXICOSIS

Introduction

THE term hyperthyroidism indicates hyperactivity of the thyroid gland and hypersecretion of its essential hormone thyroxine. Thyrotoxicosis is used clinically as a synonym for hyperthyroidism.

The main clinical classification of thyrotoxicosis is into primary and secondary thyrotoxicosis. In the former the symptoms are noticed at the same time as the thyroid gland becomes enlarged; in the latter a symptomless goitre has been present for some years before toxic symptoms become apparent. Primary thyrotoxicosis is also known as exophthalmoic goitre because exophthalmos is so characteristically a feature and secondary thyrotoxicosis as toxic adenoma because the gland may show single or multiple adenomas and is frequently nodular. It, however, must be recognized that many pathologists, while recognizing the characteristic uniform hyperplasia in primary thyrotoxicosis and the tendency to nodular adenomatous formation in secondary thyrotoxicosis, also find many intermediate and mixed types of thyroid pathology which they are quite unable to divide into two distinct types or to correlate with the clinician's differential diagnosis. Nevertheless the symptomatology, response to treatment and prognosis, as well as the age incidence, do suggest a basis for clinical diagnosis which is indicated below in tabular form.

Exophthalmic Goitre	*Toxic Adenoma*
Thyroid swelling and symptoms appear simultaneously (primary thyrotoxicosis)	Thyroid swelling may precede symptoms by a period of years (secondary thyrotoxicosis)
Any age, often less than 35	Usually over 40
Smooth diffuse thyroid enlargement	Nodular thyroid enlargement

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CHAPTER XXI

EXOPHTHALMIC GOITRE

(Graves s Parry s Basedow s Disease)

(a) Definition

Exophthalmic goitre is primary thyrotoxicosis or hyperthyroidism usually associated with exophthalmos and a diffuse enlargement of the thyroid gland

(b) Nomenclature

C H Parry a Bath physician observed one case in 1786 and published eight cases in 1825 P J Graves a Dublin physician described three cases in 1835 Basedow of Messeburg a small town near Leipzig described four cases in 1840 His description was more detailed than previous ones and in Germany his name is always associated with the disease Few diseases can have had more synonyms and none more eponyms (Rolleston)

(c) Incidence

Exophthalmic goitre is much more common in women than men the proportion being 8 to 1 It is most frequent among young women but may occur at all ages including childhood and old age

(d) Pathology

Diffuse hyperplasia with high columnar cells in layers (often plicated) and little or no colloid is characteristic with active mitosis in progress Multiple adenomas may occur and even areas of colloid filled vesicles with flattened epithelium A generalized hyperplasia of lymphatic tissue (including that in the thyroid itself) and hyperplasia of the thymus gland are often found The liver may show areas of necrosis or atrophy and is often depleted of glycogen

Foss and others found that in eleven cases dying in thyroid crisis unassociated with a precipitating infection or with complications neither the condition of the heart liver nor thymus seemed to be the constant cause of death although changes were frequently found in all these organs Thus the heart

Exophthalmic Goitre	*Toxic Adenoma*
Exophthalmos usual and often severe	Exophthalmos slight or even absent
Lid retraction often prominent	Lid retraction usually slight
Nervous and emotional symptoms prominent occasionally with tendency to maniacal excitement	Nervous symptoms not prominent
Simple tachycardia but auricular fibrillation occurs—usually late	Tachycardia relatively more severe with auricular fibrillation frequently superimposed
Recurrence after thyroidectomy 6 5 per cent or more	Recurrence after surgery less than 1 per cent

Plummer suggested that in exophthalmic goitre there is an abnormal secretion (dysthyroidism) whereas in toxic adenoma there is only an excess of the normal secretion (hyperthyroidism) he also believed that a toxic adenoma is relatively insusceptible to iodine but his views have failed to find general acceptance More recently it has been claimed that the response to thiouracil is much greater in exophthalmic goitre than in toxic adenoma but this supposed response differentiation is certainly not absolute or constant in my experience Nevertheless experience tends to support a clinical differentiation based on the criteria in the above table although at times these might appear more relative than absolute Unfortunately such a differentiation cannot always be sustained on pathological grounds Thus an enlarged thyroid that is smooth and uniform on clinical examination might subsequently be found to contain several adenomas whereas a nodular goitre might contain areas of hyperplasia identical with that of exophthalmic goitre

that whereas infection apparently increases the activity of a hyperfunctioning gland e g exophthalmic goitre it decreases



FIG 4 EXOPHTHALMIC GOITRE Woman aged 34 typical case

the efficacy of a hypofunctioning gland e g pancreas para thyroid posterior pituitary)

Since psychical trauma sexual maladjustment and infection are of such common occurrence it must be postulated that exophthalmic goitre is unlikely to follow unless there is a thyroid diathesis This view receives some support from the fact that there is a tendency for the disease to occur in families In fact a wide view of disease suggests that psychoneuroses may

often showed hypertrophy myocardio fibrosis and occasionally coronary disease but in three patients the heart was normal One liver was normal but in ten livers areas of central necrosis were found and eight showed fatty degeneration Hypertrophy of the thymus was usual but not invariable They conclude that the pathologist has cast no definite light on the pathogenesis of *crisis*

(e) Aetiology

The cause is unknown but psychical trauma sexual maladjustments or infection frequently appear to precede or initiate the symptoms Emotional stimuli might act via the hypothalamus and the pituitary thyrotropic hormone and experimentally the latter does produce thyroid hyperplasia and hyperthyroidism However it has not been unequivocally demonstrated that thyrotoxic patients have a high concentration of thyrotrophic *hormone in their blood* and in those conditions where excess of pituitary thyrotrophic hormone might well be anticipated e g acromegaly and Cushing s syndrome (when primarily pituitary in origin) clinically thyrotoxicosis is rare whereas colloid goitre without thyrotoxicosis is not uncommon On the other hand in Graves s disease the tendency of the residual portion of the thyroid gland to undergo hyperplasia with resulting recurrence of hyperthyroidism after incomplete thyroidectomy does suggest an extra thyroid stimulus the most likely being the pituitary thyrotrophic hormone Sympathetic nerve stimulation is inadequate experimentally to produce thyroid hyperplasia and hyperfunction Physiological enlargement of the thyroid is not uncommon at puberty at the menopause or during pregnancy and this may proceed to characteristic exophthalmic goitre Sexual difficulties may precipitate or cause hyperthyroidism by virtue of a close gonadal thyroid or gonadal pituitary interrelationship but more probably they constitute only another form of psychical trauma or psychoneurosis The influence of infection is suggested by the disease appearing for the first time during an acute infection but this may be more apparent than real since infection is known to aggravate a pre existing hyperthyroidism Experimentally however it can be shown that *staphylococci* render the thyroid hypersensitive to the stimulus of the pituitary thyrotropic hormone (It is interesting to note

(ii) *Cardiovascular* The heart rate and pulse rate are almost invariably raised and in contradistinction to some forms of functional tachycardia the rapid rate persists during sleep Teleologically this serves the purpose of meeting an increased oxygen requirement the stroke volume and arteriovenous oxygen difference usually remaining unchanged The cause of the tachycardia however is the increased secretion of thyroxine and the condition can be produced experimentally by thyroid feeding In the latter condition there is also an increased sensitivity of the heart to injections of adrenaline so that this is probably true in thyrotoxicosis also Extra systoles and paroxysmal sinus tachycardia may also be met with and in older patients or in cases of long standing auricular fibrillation supervenes The latter is said to be more frequent with toxic adenoma than with primary thyrotoxicosis but this may well be explained by the age incidence Auricular fibrillation may supervene in the post operative period after thyroidectomy when normal rhythm was present before operation Angina and congestive heart failure are other cardiac complications of thyrotoxicosis

The systolic pressure is usually raised and the diastolic frequently below normal so that a large pulse pressure is characteristic The diastolic pressure may appear to be zero by the auscultation method As in aortic incompetence this large pulse pressure may be associated with capillary pulsation The vasomotor system is unstable and paroxysmal vasodilatation is shown by flushing of the face and neck in a warm atmosphere or during excitement as also occurs at the climacteric It has recently been suggested that certain cases of hypertension are of thyroid origin but this diagnosis must be accepted with caution should the diastolic pressure be appreciably raised and the pulse pressure normal

Electrocardiographic changes occur in some 30 per cent of patients and characteristically consist of tall P and T waves and low or slurred R waves findings which have also been reported with a high sympathetic tone A prolonged P–P interval may also be found Radiologically cardiac enlargement is found in some 30 per cent of patients It is usually to the left and the pulmonary arc and right auricle may be prominent It is claimed that in some patients with auricular

produce duodenal ulcer effort syndrome (or disordered action of the heart) hyperidrosis dyspareunia achalasia of the cardia and possibly Raynaud s disease but that in all these conditions a constitutional local abnormality or hypersensitivity determine the characteristic manifestation However it would be unwise to conclude that hyperthyroidism might not be in some cases a spontaneous outburst of endocrine hyperactivity for which we have not yet found an adequate explanation A relative or absolute deficiency of iodine is one possible aetiological factor but this is more appropriately considered in the goitre and toxic adenoma sections The discovery of the goitrogenic action of such substances as thiourea found in vegetable food stuffs and ergothioneine a normal constituent of blood raises the possibility of another cause of hyperplasia but such hyperplasia is associated with hypothyroidism rather than hyperthyroidism (see Thiouracil section)

(f) Clinical Picture

(1) *General* Fear anxiety restlessness and instability are the characteristic symptoms but in early manifestations the patient may only show a vivacity and dynamic spontaneity—almost an accentuation of pleasing feminine characteristics—and the slight *exophthalmos which gives a glint and coquettish look to the* eye is not unattractive These symptoms are associated with an over activity of the sympathetic nervous system which is sensitized by thyroxine

Exophthalmos tremor tachycardia increased metabolism loss of weight and thyroid enlargement are the cardinal symptoms *The thyroid enlargement is usually diffuse involving* both lobes and the isthmus but often asymmetrically A bruit is heard on auscultation Occasionally no obvious enlargement is detectable clinically This may be due to the thyroid gland being more deeply situated than is usual or to its being placed retrosternally Enlargement of the thyroid gland if situated in the neck is best detected with the patient lying flat without a pillow and gentle pressure on one side of the trachea when the opposite lobe if enlarged can usually be palpated and vice versa The tremor is a fine one revealed by extending the hands It is often unknown to the patient but may be very obvious on holding a pen or pouring out water

ptosis and enophthalmos The fact that the pupils in thyrotoxicosis are not usually dilated does not contra indicate the sympathetic mechanism of upper lid retraction since such experimental dissociation can be produced by appropriate dosage



FIG 48 GRAVES'S DISEASE In a male aged 36 to illustrate unilateral exophthalmos and lid retraction

Both experimentally and clinically the condition may be asymmetrical in degree or completely unilateral for a period so the additional factor of local responsiveness must be postulated Thyroid feeding occasionally produces lid retraction but it is a rarity It is important to remember that abolition of the thyrotoxicosis will abolish upper lid retraction and the latter does not occur with myxoedema

Exophthalmos is a different story and a more complex one Experimentally in some species it may be produced in moderate degree by thyroid feeding or sympathetic stimulation It is probable that this is true also in man although actual records

fibrillation and thyroid enlargement the latter condition may be aetiological even when the basal metabolic rate is normal and that thyroidectomy will cure the condition It is imprudent to ascribe any cardiac abnormality or any hypertension to hyperthyroidism in the absence of a raised basal metabolic rate especially if the latter is not relatively lowered by iodine medication Total thyroidectomy however has been advocated and temporary success claimed in some 50 per cent of patients with congestive heart failure or angina in the absence of any thyroid disorder The heart becomes less sensitive to adrenaline and the different nerve impulses are interrupted and these two factors explain more immediate benefit but the duration of the effect is dependent upon the maintenance of a subnormal metabolism and concomitant diminished cardiac requirements

(iii) *Ocular signs* There are a number of classical signs descriptive of ocular abnormalities in thyrotoxicosis which are of historical and examination interest

von Grafe s sign On looking down slowly the upper eyelid lags behind so that the white sclerotic becomes visible above the pupil

Joffroy s sign On looking upwards there is no wrinkling of the forehead (occipito frontalis muscle)

Stellweg s sign Absence or infrequency of blinking

Mobius s sign Inability to converge or sustain convergency

Dalrymple s sign Wide palpebral fissure

It is advisable however from the point of view of aetiology and of prognosis to differentiate two conditions (1) upper lid retraction (2) exophthalmos The former is manifested by the relationship of the upper edge of the iris to the upper eyelid and the latter by the relationship of the lower edge of the iris to the lower lid in both cases the more severe degrees being shown by an intervening white sclerotic area Upper lid retraction is produced by cervical sympathetic stimulation (contraction of Muller s palpebral muscle) or by sympatho mimetic drugs e g adrenaline which act on the neuromuscular junction even when the sympathetic nerve is sectioned *Thyroxine* sensitizes the end organ to such stimulation as it does in other sites e g the heart Experimentally upper lid retraction is usually but not invariably associated with dilatation of the pupil Section of the cervical sympathetic nerve is followed by

ever involve the sympathetic neuromuscular junction In any case clinically it is important to remember that one cannot promise relief of exophthalmos in thyrotoxic patients by thyroidectomy or other radical measures It is not the usual practice to carry out a cervical sympathetic ganglionectomy in the earlier stages and in the later stages it is unhelpful the only measures then available being mechanical e g tarsorrhaphy Other possible means of counteracting a thyrotrophic stimulus would be deep radiation of the pituitary gland or inhibition of its activity by oestrogens androgens or thyroid As yet insufficient evidence is available as to the efficacy of these measures

It is interesting to note that exophthalmos although due to a central or hormonic stimulus is often asymmetrical in degree and not infrequently affects one eye before the other It may be associated with oedema of the eyelids

Ophthalmoplegia associated with exophthalmos first described by Naumann in 1853 and recently studied by W R Brain may occur with severe thyrotoxicosis with post thyroidectomy myxoedema with mild thyrotoxicosis or with no obvious thyroid dysfunction It is thought to be due to a pituitary thyrotrophic stimulus comparable to the condition which can be experimentally produced by injections of thyrotrophic hormone even after thyroidectomy The histological picture of the extraocular muscles is similar whether or not thyroid dysfunction is present—namely swelling oedema foci of lymphocytic infiltration and in the later stages fibrosis Clinically the condition tends to occur in the forties or fifties and there is only a slight preponderance of females It is usually asymmetrical in onset and degree The paraplegia tends to affect groups of muscles responsible for particular movements e g elevation or lateral movement rather than individual muscles Brain believes the ophthalmoplegia is mainly a mechanical effect of the exophthalmos Widening of the palpebral fissure with retraction of the upper eyelid is not infrequent but there may be ptosis A marked degree of oedema of the peri orbital tissues is present in all severe cases but papilloedema is exceptional Some pigmentation of the orbits and leucoderma of the limbs are occasional associations Exophthalmos is often refractory to treatment and may be progressive Methods of dealing with it are considered later under the heading Malignant Exophthalmos

of it resulting from thyroid feeding in man show that it is exceptional. However sympathetic nerve sensitivity produced by thyroxine may play a part in thyrotoxicosis by the contraction of intra orbital smooth muscle producing exophthalmos and also obstructing venous return with resulting oedema of orbital muscles. Clinical experience however shows that such sympathetic nerve stimulation is not the major cause since, unlike upper lid retraction, abolition of thyrotoxicosis by radical measures does not abolish exophthalmos and may even increase the degree. Some measure of improvement may be obtained if cases are treated early enough e g by thyroidectomy and this slight improvement is probably a measure of the small part played by sympathetic nerve stimulation after sensitization by thyroxine

Light has been thrown on the aetiology of exophthalmos by the fact that pituitary thyrotrophic hormone will produce the condition in the absence of the thyroid gland. This is paralleled clinically by the exacerbation of exophthalmos or by its initial appearance after a too radical thyroidectomy, which has resulted in a myxoedematous state. (One possible flaw in the theory is that exophthalmos is not usually found with sporadic or endemic myxoedema although there is a hypersecretion of thyrotrophic hormone in myxoedema as there is of gonadotrophic hormone in hypogonadism.)

In earlier experiments Marine showed that the goitrogenic substance methyl cyanide would produce exophthalmos as well as hyperplasia of the thyroid gland but that it was equally effective after thyroidectomy. He postulated that this resulted from a secretion of thyrotrophic hormone and that the exophthalmos resulting from hypothalamic stimulation was produced in similar fashion. In both cases the effect was abolished by removing the cervical sympathetic ganglia but dividing the cervical sympathetic nerves was only partially successful. In human beings such measures are without success but this may be due to local secondary irreversible changes e g oedema and lymphocytic infiltration of the ocular muscles with muscular degeneration and fibrosis. Until it is established that thyrotrophic hormone cannot produce exophthalmos in the absence of the cervical sympathetic ganglia I think it prudent not to exclude the possibility of a more direct action which may how

(iv) *Metabolism* The essential action of the thyroid gland is an acceleration of metabolism as was first shown by Magnus-Levy in 1895 With exophthalmic goitre the basal metabolic rate is always raised The test which is carried out as a routine in the United States of America and in many clinics in this country is a very valuable aid to scientific observation of the course of events It must be admitted however that it is rarely a diagnostic necessity and this is also true of the various substitution mathematical formulae

The increased metabolism is evidenced by the negative nitrogen balance the loss of weight and the increased appetite which often becomes ravenous patients may nevertheless progressively lose weight owing to the preponderance of catabolism over anabolism All elements of food are involved the liver is depleted of glycogen the fat depots of the body tend to disappear and the negative nitrogen balance together with creatinuria indicate the breakdown of muscle tissue Another manifestation of increased metabolism is ability to stand cold and an intolerance of heat Some degree of pyrexia is not infrequent especially with slight infections Hyperglycaemia and glycosuria are not uncommon being probably due to the acceleration of glycogenolysis in the liver by adrenaline and the sympathetic nerves thyroxin renders the hepatic cells sensitive to such influences True diabetes mellitus is probably not more common among exophthalmic goitre patients than among normal individuals

The blood cholesterol values may be subnormal e g 80 mg (normal 150 to 190) in contrast to the raised values in myxoedema Excretion of sodium and chloride (as occurs to a greater extent in Addison s disease) may also be increased and this may partially explain the loss of strength disproportional to the wasting

(v) *Calcium and phosphorus metabolism* Demineralization of the skeleton and softening of the bones in hyperthyroidism was first observed by von Recklinghausen in 1891 while doing an autopsy Although a spontaneous fracture in thyrotoxicosis is infrequent rarefaction of bones is not uncommonly seen during systematic radiographic examination of thyrotoxic patients and the negative calcium balance revealed by biochemical studies drew attention to the frequency of a disturbed calcium and phosphorus metabolism in thyrotoxicosis



Fig 49 Graves's Disease To illustrate immediate change in the glint of the eyes due to abolition of upper lid retraction —photograph taken weeks after thyroidectomy Lid retraction as distinct from exophthalmos is nearly always abolished by thyroidectomy

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Most of the original biochemical work was carried out by Aub and collaborators who found normal serum calcium and phosphorus values (occasionally slightly lower than normal) but a *negative calcium balance with the calcium loss predominately in the faeces* there is also a moderate elevation of serum phosphatase values Successful thyroidectomy tended to abolish these findings although as with parathyroidectomy for hyperparathyroidism the biochemical reversion to normality was *early but the recalcification of bone often delayed* Since a positive calcium balance is found in myxoedema and since experimentally, thyroid extract produces a negative calcium balance it seemed probable that the disturbance of calcium and phosphorus metabolism was entirely due to excessive thyroxine secretion However Beaumont Dodds and Robertson found that in 50 per cent of thyrotoxic patients calcium and phosphorus metabolism was normal there was no relationship between the degree of negative calcium balance and the severity of thyrotoxicosis and successful thyroidectomy might leave the disturbance of calcium metabolism unchanged They concluded that there was another factor involved in some cases and in fact Hansman and Wilson had previously postulated a coexistent hyperparathyroidism Clinically both rarefaction of bones and spontaneous fractures *occasionally* occur several years after successful thyroidectomy and with a normal basal metabolic rate We must conclude that excessive thyroxine secretion produces a negative calcium balance and decalcification of bones in thyrotoxicosis but that in some patients there may be a co existing hyperparathyroidism

(vi) *Behaviour and emotion* The patient is restless and anxious In spite of physical weakness general interests and activities are multiple There is however an inability for sustained concentration and effort is desultory Sensibilities are acute and perceptual and intellectual processes often above normal Patients are apt to be talkative and full of ideas Emotional reactions are characterized by instability A psychiatrist might label many such patients neurotic and a psychosis occasionally develops

(vii) *Sex function* Disturbances of menstruation and pregnancy in thyrotoxicosis might be anticipated from the evidence discussed in the physiological section Menstruation is often

normal in mild degrees of thyrotoxicosis but in more severe cases oligomenorrhoea or amenorrhoea occurs in more than 50 per cent of patients A return to normal menstruation after thyroidectomy is usual but not invariable Menorrhagia is a rarity Impotence in males may be met with and may respond to testosterone

In animals it is physiological for the thyroid gland to enlarge during pregnancy and the mechanism is through the pituitary thyrotrophic hormone The thyroid gland becomes palpable in some 30 per cent of pregnant women and the basal metabolism is raised to plus 35 per cent in most women in the last trimester of pregnancy but clinical hyperthyroidism is not usual Nevertheless thyrotoxicosis does occur in 1 4 per cent of pregnant women and from the facts that occasionally it is manifested temporarily in successive pregnancies and that a pre existing goitre may become toxic during pregnancy, it would appear that pregnancy may be a precipitating factor Marine found that there was a relative iodine deficiency during pregnancy and that minute amounts of iodine usually prevented or controlled thyroid enlargement It is interesting to note that when thyrotoxicosis becomes evident during pregnancy the thyroid enlargement may be nodular or diffuse and that histological section may show a nodular colloid goitre with areas of glandular hyperplasia When pregnancy supervenes on a pre existing hyperthyroidism the latter condition may not change in severity or may be ameliorated but sometimes there is a severe exacerbation especially in the latter months Abortion is contra indicated except perhaps in the first 2 months as a thyroid crisis may thereby be precipitated For relatively mild cases iodine and sedative medical treatment may be sufficient For more severe cases more radical measures e g thyroidectomy are advisable Deep radiation and thiouracil have their place (see Therapeutic section) and in general the principle is treat the thyrotoxicosis and not the pregnancy If thiouracil is used in pregnancy it is advisable to replace it by iodine in the last month as experimentally the offspring may be born with enlargement of the thyroid and hypothyroidism In the few pregnant patients treated up to date there was enlargement of the thyroid in only one infant and this disappeared in 3 months There was no clinical evidence of thyroid dysfunction

Attempts to ameliorate thyrotoxicosis in non pregnant women with large doses of oestradiol, on the theory that the secretion of pituitary thyrotrophic hormone would be thus inhibited, have failed and not unexpectedly

(viii) *Gastro intestinal tract* Gastro intestinal symptoms occur in some 30 per cent of patients of which diarrhoea abdominal discomfort after meals and nausea are the commonest Intractable vomiting may precede a crisis Epigastric pain may simulate that of gastric ulcer and occasionally the latter is a complication Upper abdominal pain may rarely be sufficiently acute and severe in its onset to simulate an acute abdomen but in one such case hyperaemia of the pancreas was found on laparotomy Achlorhydria is not infrequent and radiological findings (R B Brown and others) are prominence of gastric rugae early gastric emptying but delay in completion of this increased intestinal tone and movement both in the small and large intestine All these changes may be produced experimentally by thyroid feeding and tend to disappear after a successful thyroidectomy for thyrotoxicosis Atrophic gastritis may be found at autopsy Occasionally the presenting features are gastro intestinal this constituting a variety of forme fruste

(ix) *Other symptoms* Troublesome perspiration sometimes very profuse results from sympathetic nervous stimulation and increased metabolism This is associated with a pathological thirst which may never be adequately satiated especially in warm weather

Crisis An acute exacerbation of all the symptoms may occur spontaneously or be precipitated by some infection The manifestations may be predominatingly cardiac (tachycardia) cerebral (acute mania delusions delirium), or gastro intestinal (diarrhoea and vomiting) In the last mentioned condition, abdominal pain severe enough to simulate an acute abdomen is often present and laparotomy performed The pancreas is acutely congested (as in mumps) and this may explain the symptoms in some instances

(g) Thyrotoxicosis in Children

This condition is comparatively rare less than 1 per cent of all cases of thyrotoxicosis occurring in children under 12 but as much as 5 per cent occurring in children under 16 There is

therefore an abrupt rise in incidence at puberty which like pregnancy and the climacteric may precipitate thyrotoxicosis There is a familial incidence in thyrotoxicosis and Cockayne believed the thyroid diathesis to be an irregular Mendelian dominant The case of Osterreicher in which a woman with chronic thyrotoxicosis gave birth to 10 children of whom 8 subsequently developed thyrotoxicosis is however an extreme example of its familial incidence A positive family incidence of thyrotoxicosis including adults is found in some 20 per cent of all cases but rarely involving more than 2 or 3 members of the existing generation In juvenile thyrotoxicosis girls are affected about five times more frequently than boys The treatment is the same as for adults except that in relatively mild cases symptomatic treatment is more likely to be successful than in adults and an expectant attitude is often justified

(h) Diagnosis

Usually this is obvious clinically to an observer not lacking in awareness of the condition but occasionally one of the symptoms may be so obtrusive as to hide the underlying basic condition of thyrotoxicosis In these circumstances the term forme fruste is used a name originally applied by Marie in 1883 to those forms of thyrotoxicosis in which exophthalmos and enlargement of the thyroid were minimal or clinically undetected In such atypical cases as in other instances of forme fruste the initial diagnosis may be congestive heart failure angina pectoris auricular fibrillation arterial hypertension effort syndrome (D A H) diabetes mellitus gastro intestinal disturbance, pulmonary tuberculosis idiopathic or malignant wasting psychoneurosis psychosis acute thyrotoxic bulbar palsy myasthenia gravis or progressive muscular atrophy

A detailed differential diagnosis of all these conditions would serve less purpose than a plea for increased awareness of the possibility of an underlying thyrotoxicosis especially since the majority of these conditions are possible manifestations or complications of thyrotoxicosis True myasthenia gravis and progressive muscular atrophy are rarely present but may be simulated A form of the latter apparently directly related to the thyrotoxicosis is called chronic thyrotoxic myopathy and another variety usually fatal acute thyrotoxic bulbar palsy

Hypertension associated with a considerably raised diastolic pressure is unlikely to be due to thyrotoxicosis, although some cardiologists claim otherwise In this as in other conditions mentioned above the abolition of thyrotoxic symptoms by successful thyroidectomy is often disappointing in its failure to relieve a coincident but not directly related condition True myasthenia gravis associated with thyrotoxicosis and responding to prostigmine may however be appreciably relieved by thyroidectomy and this may be explained by the resulting involution of a coincident thymus and lymphoid hyperplasia since thymectomy is of value in non thyrotoxic myasthenia gravis

Occasionally a case of idiopathic coma turns out to be of thyrotoxic origin and I have seen one such case in which autopsy findings were those of thyrotoxicosis and there was hyperaemia of the brain and meninges but no other explanation of the comatose condition The patient had probably had the thyrotoxicosis for some time but without seeking medical advice, and died within a few hours of admission to hospital in a state of coma of acute onset without any clinical history being available Zondek has also described such cases

Disordered action of the heart or effort syndrome is often mistaken for hyperthyroidism and especially as there may be a coincident enlargement of the thyroid gland The tachycardia however is more variable than that of thyrotoxicosis and the pulse rate varies with change of position There is also an absence of other features of thyrotoxicosis and loss of weight is rarely a feature

Rarely patients with thyrotoxicosis show pigmentation of the face and body due to an excessive deposition of melanin histologically indistinguishable from that of Addison s disease although the mucous membranes are never involved It seems however that the adrenal cortex must be functionally disturbed in such cases and occasionally there is a coincidence of thyrotoxicosis and Addison s disease in the one patient

In general where the clinical diagnosis is not certain extra help may be obtained by laboratory aids e g raised basal metabolic rate subnormal serum cholesterol values impaired oral galactose tolerance curves and low blood protein bound iodine concentration

There are several methods of determining the basal metabolic

rate and the Benedict-Roth and Jones's apparatuses among others are in my experience satisfactory It is not necessary to



FIG 50 THYROTOXICOSIS with wasting For some time the underlying pathology was unsuspected

hospitalize the patient and if no food has been taken and the patient rests for half an hour before the test the results are consistent and clinically satisfactory The lowering of the basal metabolism following iodine therapy is useful confirmation of the diagnosis especially when the initial basal metabolism is not appreciably raised Blood cholesterol values below 100 mg per 100 c c strongly support the diagnosis of thyrotoxicosis and values over 200 mg make it unlikely

(i) Course and Prognosis

The natural course of the disease is progressively downhill but waves of remission and exacerbation occur Apart from any specific treatment recovery occasionally occurs and even myxoedema may eventually develop

Treatment by radical measures e g thyroidectomy radiation or thiouracil produces cure or a very high degree of amelioration in some 70 per cent of patients The remainder are improved sufficiently to lead a quiet existence A small percentage perhaps 5 per cent remain uncontrolled or have serious remissions whatever treatment is adopted Even in those who are greatly improved some residual evidence of a pre existing hyperthyroidism may remain e g exophthalmos neurosis or auricular fibrillation Some patients become very fat even when the thyrotoxicosis is incompletely controlled and this appears to be due to secondary changes in the anterior pituitary gland Where treatment has been too radical myxoedema develops

More conservative medical treatment e g sedatives and iodine may be effective in mild degrees of thyrotoxicosis if carried out over a sufficiently long period as the disease may run a self limited course but one can never be sure that there may not develop an acute exacerbation calling for radical treatment Such measures should not be delayed where there is danger of irreversible harm to the cardiovascular system the eyes *or the personality*

(j) Treatment

Since in my opinion the application to thyroto*xicosis* by Astwood of the Mackenzies experimental work on thiouracil is a dramatic development in the treatment of thyrotoxicosis I propose to give this first place in this therapeutic section although older medical and surgical methods in suitable cases are by no means obsolete and are not likely to become so

(i) *Thiouracil* Thiourea and thiouracil have similar action but thiourea has been discarded clinically in preference to thiouracil since the former produces malodour of the breath and is not infrequently nauseating In the physiological section it has been indicated that thiouracil acts by preventing the synthesis *of thyroxine* It is suggested that this is achieved by blocking the normal iodination of protein concerned in the pro

duction of active thyroid hormone or by reducing peroxidase activity in the thyroid and thus preventing the conversion of diiodotyrosine to thyroxine Histology and biochemical assay show that thiouracil prevents the taking up of iodine by the thyroid gland and the storage of iodine as intravesicular colloid for even when some colloid is present it is poor in iodine content Blood iodine studies show that the use of thiouracil is followed by a fall in the protein bound iodine of the blood to normal or subnormal limits The hyperplasia of the thyroid gland that results from thiouracil is produced by excessive secretion of pituitary thyrotrophic hormone and may be associated with resulting enlargement of the thyroid gland

Thiouracil is available in tablets of 100 mg and the usual initial dosage is 200 mg three times a day The average patient shows clinical signs of response in 1 to 2 weeks but in a small proportion of cases the dosage must be increased to 200 mg five times a day before a favourable response is seen Thiouracil is a potent drug producing toxic effects in some patients sensitive to it (some 10 per cent or more) and in large doses even in patients not especially sensitive It is therefore advisable to use the minimum initial dose that is likely to be effective and when an adequate clinical and metabolic response has been obtained e g after 3 weeks to reduce the dosage to 100 mg daily or even less Himsworth has pointed out that if the patient has previously been given iodine the response to thiouracil is initially slight and may be delayed for many weeks so that it is advisable to stop iodine therapy for some weeks before commencing with thiouracil This is explained by the fact that the thyroid gland has stored thyroxine and continues to secrete it despite treatment One also meets with cases of primary thyrotoxicosis which even in the absence of pre iodine medication nevertheless show an inadequate or delayed response to thiouracil but which after continuing with small doses of thiouracil e g 100 mg daily over long periods e g 3 months will ultimately show completely adequate results (personal observation) This is reminiscent of the delayed results sometimes seen after deep radiation of a hyperplastic thyroid and also of the relatively delayed response of toxic goitre

Initial clinical improvement is shown by diminished perspiration diminished tremor and excitability *gain in weight and*

general well being The slowing of the pulse rate is sometimes a delayed response Excessive lid retraction tends to disappear but exophthalmos may persist be ameliorated, or occasionally as after thyroidectomy increase This is explained by the fact that exophthalmos as distinct from lid retraction is largely due to the secretion of pituitary thyrotrophic hormone and we have observed that thiouracil produces an excessive secretion of thyrotrophic hormone For the same reason the thyroid gland does not initially decrease in size and may even become larger and even cause pressure and discomfort Nevertheless, it would appear that after continued therapy over 6 months or more both the degree of exophthalmos and the size of the thyroid usually tend to decrease although there are exceptions to this and both exophthalmos and goitre may persist or increase in the presence of a thiouracil produced myxoedema

Concomitant with the clinical improvement after 7 to 21 days of thiouracil treatment there is a decrease in the basal metabolic rate and an increase in blood cholesterol and normal or subthyroid values may ultimately result The increase of weight is sometimes relatively early and excessive and disproportionate to other objective and subjective criteria and I have suggested that this may be associated with changes produced in the anterior pituitary gland

As to the duration of treatment Astwood found that in 50 per cent of patients treatment with thiouracil could be discontinued after some 6 months without relapse following but that in the remaining 50 per cent relapse followed rapidly and continued until thiouracil was resumed Since thyrotoxicosis may after many years of symptomatic treatment eventually give way to myxoedema it may well be that after a long period of thiouracil thyroid hyperplasia some degree of exhaustion atrophy will result This appears to occur in the tadpole

Toxic effects occur in some 10 per cent of patients receiving thiouracil and the most serious of these is agranulocytosis which may prove fatal if undetected in the early stages by systematic blood examination Therefore every patient treated with thiouracil should have an initial blood count and then leucocyte counts every week for the first 6 weeks and then once a month, and also immediately if the clinical condition changes for the worse as indicated for example by malaise sore throat

and/or pyrexia Although a sensitivity to thiouracil is shown usually within the first 4 weeks by a lowering of the total leucocytes and of the percentage polymorphonuclear leucocytes this effect may be a delayed one and not evident for some months Should these values be reduced below some 40 per cent of the normal it is an indication for ceasing thiouracil therapy or reducing the dosage to a minimal one In many cases of thyrotoxicosis before treatment there is an initial leucopenia and relative lymphocytosis These findings are not a contra indication to thiouracil which may in fact produce a more normal white cell picture Other manifestations of the toxicity of thiouracil are thrombocytopenia generalized enlargement of lymph glands and of the spleen fever nausea and vomiting dermatitis arthralgia jaundice and general malaise Nevertheless in the majority of patients and under careful control including blood counts basal metabolism and blood cholesterol estimations thiouracil is a very valuable means of dealing with thyrotoxicosis It is of little or no value as a substitute for complete thyroidectomy in heart trouble unassociated with thyrotoxicosis

Addendum Methyl thiouracil is less toxic than thiouracil and is tending to replace it in practice the dosage being the same Propyl thiouracil has been found to be more active and less toxic than thiouracil the dosage being rather less than that of methyl thiouracil (Astwood and Van der Laan 1945)

I have found that the supplementary use of Lugol s iodine permits minimal doses of methyl thiouracil to prove effective The discovery that ergothioneine a normal constitutent of blood has a similar action to thiouracil in animals (Lawson and Rimington 1947) is of great interest

(ii) *Thyroidectomy* Thyroidectomy is indicated in the following types of case (1) when the patient favours a direct and rapid attack on the disease (2) when the patient is sensitive to thiouracil (3) when medical treatment appears to offer little hope in the presence of severe thyrotoxicosis (4) when pressure symptoms are present or the thyroid enlargement is very considerable (5) when auricular fibrillation is present although in suitable cases thiouracil has produced a return to normal rhythm or a responsiveness to quinidine

Pre operative preparation with iodine introduced by Plummer of the Mayo Clinic has rendered surgery in skilled hands

safe the mortality being 0 1 per cent Iodine is usually given in the form of Lugol s iodine 5 to 10 minims three times daily for 7 to 10 days prior to operation as this period appears to coincide with the maximum amelioration that can be produced by iodine It is advisable to give 1 drachm of Lugol s iodine in rectal saline once daily for the first few days after operation and it is then my practice to continue with 5 minims of Lugol s iodine daily by mouth for some 6 weeks or longer in the belief that this prevents excessive hyperplasia of the remnant of thyroid gland left behind by the surgeon It is now evident that thiouracil affords a better preparation for thyroidectomy in severe thyrotoxicosis than does iodine It, however pro duces a very vascular gland which can be obviated by stopping the thiouracil when metabolism is normal and substituting Lugol s iodine ten days before thyroidectomy If given with thiouracil iodine appears to augment its action but the gland remains vascular If given previously to thiouracil iodine pro duces by colloid storage a delayed response to thiouracil The surgeon removes some seven eighths of the thyroid gland leaving a posterior layer that will prevent interference with the parathyroid glands embedded behind Nevertheless tetany occasionally supervenes and serial sections of the removed thy roid gland demonstrate that in the majority of such cases the tetany is not due to removal of parathyroid glands and therefore probably due to interference with blood supply It is usually transitory and its treatment is indicated in the Tetany section (It should be noted that although Plummer introduced iodine in the pre operative preparation for thyroidectomy its beneficial effects on thyrotoxicosis were initially observed by Trousseau who prescribed it in error for digitalis in one of his thyrotoxic patients)

(iii) *General medical treatment* This consists of sedatives and iodine For the former I use phenobarbitone gr $\frac{1}{4}$ to $\frac{1}{2}$ t d s as there is some evidence that it decreases sensitivity to thy roxine Bromides and quinine hydrobromide are also used and the latter is said to have some specificity Iodine appears to act by storing thyroxine as intravesicular colloid and thus diminish ing its secretion Although its maximum effect tends to occur about the tenth day of its use it still remains of value and in my experience determines that the disease of thyrotoxicosis

runs its course at a lower level than would otherwise be the case At the Mayo Clinic I found that Boothby used small doses of iodine e g 3 minims of Lugol s iodine daily over long periods in relatively mild cases and I have continued this practice with similarly satisfactory results where more radical measures were not looked upon with favour Iodine may also be prescribed as iodicin tablets (B W & Co) a 30 mg tablet being equivalent to 2 minims of Lugol s iodine or as diiodotyrosin tablets as suggested by Harrington 100 mg tablets being equivalent to 5 minims of Lugol s iodine It is doubtful if there is any essential difference in the qualitative action of the various forms of iodine

Specific antisera have also been advocated based on the experimental fact that animals immunized with thyroglobulin are subsequently refractory to injections of thyroglobulin and may even become myxoedematous and it is claimed (Lerman 1942) that the antibodies are organ specific rather than species specific No convincing clinical results have been reported and on general grounds the method appears to be inferior to other therapeutics available

Insulin in small doses with meals or with glucose by mouth has an anabolic effect where there has been much loss of weight Testosterone is also of some value in this connexion producing water and nitrogen retention and was first used by the writer in thyrotoxicosis It however has no fundamental effect on the course of the thyrotoxicosis

Since thyrotoxicosis is often preceded by or associated with an anxiety neurosis some form of psychotherapy is often indicated Reassurance and suggestion and a willing ear are often adequate and psycho analysis is rarely required In any case such measures do not obviate the necessity for more specific therapy In acute mania associated with thyrotoxicosis prolonged preparation with thiouracil should precede thyroidectomy

The treatment of tachycardia and of auricular fibrillation is the removal or minimization of the causative thyrotoxicosis and before this is secured digitalis and/or quinidine are of little or no value Subsequent to thyroidectomy or thiouracil or radiation if normal rhythm does not automatically return quinidine 2 gr t d s progressively increased to gr 5 t d s will often be effective within a week Where the rhythm is very rapid and

in the presence of cardiac failure it is considered safer to employ digitalis for some weeks before trying quinidine and if quinidine fails to restore normal rhythm digitalis should be reverted to

In a thyroid crisis whether spontaneous or post operative iodine should be given in large doses e g 1 c c of Lugol s iodine intravenously in saline or per rectum 4 hourly or 5 c c of Lugol s iodine in a litre of glucose saline given by intravenous drip method An oxygen tent is of great value in a severe thyroid crisis as there is a great demand of the tissue for oxygen and the use of such a tent may prove life saving in a desperate case

Whether or not surgery is undertaken for thyrotoxicosis there is still need for the prudent physician in the pre and post operative phases

(iv) *Radiation and radio active iodine* Earlier attempts at destroying or inhibiting the thyroid gland by deep radiation were not only ineffective but often produced burning of the skin With modern technique the results are in my experience very good and provide a satisfactory alternative to other methods Radiotherapists vary in technique but it is usual to have two courses of radiation separated by several months and each course to consist of some 6 applications at 1 to 4 days intervals The treatment calls for patience and confidence and I have some times observed considerable delay in response an ultimately satisfactory result being arrived at some 6 months after the cessation of radiation when the patient and doctor were about to decide that more radical treatment was indicated Hasty or excessive dosage of radiation may produce myxoedema

Recently radiation has been produced by giving radio active iodine by mouth within a few hours of its preparation and I have seen excellent results Its effectiveness is confirmed by the occasional production of myxoedema The radio active iodine is taken up by the hyperplastic thyroid and the high speed electrons that it generates produce destruction of the surrounding thyroid tissue (Hertz and Roberts Chapman and Evans) A single oral dose is often sufficient 40 millicuries of the 12 hour isotope or 12 millicuries of the 8 day isotope Clinically the latter is proving more suitable as the smaller dose and the more gradual action eliminates radiation sickness and initial hyperaemia and swelling of the thyroid gland or transient exacerbation of the thyrotoxicosis

CHAPTER XXII

TOXIC ADENOMA OF THE THYROID

THIS condition has already been discussed in the classification especially from the aspect of differential diagnosis Some pathologists contend that there is no justification for the separation of this condition from primary thyrotoxicosis and apart from the occasional single encapsulated foetal adenoma the histological pictures may be identical and in any case yield insufficient evidence on which to postulate the clinical history and manifestations Thus although some cases of Graves's disease *will show general hyperplasia without adenoma formation* others will show multiple adenomas some being large and irregularly shaped Thus is in keeping with the general law that can be postulated in endocrinology namely that hyperplasia of an organ may proceed to adenomatous formation the latter being an additional manifestation of hyperactivity This law can be observed to operate in the adrenal cortex the pancreas the parathyroid and the anterior pituitary glands in all of which organs adenomatous formation may supervene upon or be a part of hyperplasia Experimentally it is most easily manifested in the adrenal cortex when pituitary adrenotrophic hormone is injected into an experimental animal However it is equally true that adenomatous formation without hyperplasia or hyperfunction may occur from other causes e g iodine deficiency (see Goitre section) and that at some future date hyper activity with hyperthyroidism is superimposed The histological picture may then become identical with that described above namely areas of hyperplasia and adenomas but the aetiology is different Thus while histology does not necessarily prevent a differentiation between primary thyrotoxicosis and secondary thyrotoxicosis (toxic adenoma) experimental studies and the natural history of endemic goitres suggest such a differentiation More important still is the difference between the clinical pictures and the response to the various forms of therapy

Clinical Picture

The condition occurs most frequently in women and usually

over the age of 40 Characteristically an enlargement of the thyroid without other features has been observed for some years prior to the onset of hyperthyroidism but such a sequence is not invariable at least in so far as the patients observations or absence of observation can be accepted The enlargement is usually asymmetrical and may appear to involve only a portion of one lobe However even in such cases surgical exploration often reveals more extensive involvement of the thyroid gland

The symptoms are those previously described as due to thyrotoxicosis whatever the aetiology with however four important differences

(1) Eye signs especially exophthalmos are minimal or absent This suggests that the pituitary thyrotrophic hormone does not play a big part in the aetiology
(2) The hyperexcitability emotionalism and associated anxiety neurosis of Graves's disease are usually absent or minimal and in any case are of much lesser degree than the severity of the hyperthyroidism as judged by basal metabolic rate or blood cholesterol
(3) The brunt of the thyrotoxicosis appears to fall upon the cardiovascular system auricular fibrillation being frequently superimposed upon sinus tachycardia and extrasystoles The inability of the myocardium to withstand thyrotoxicosis may be partly explained by the greater age incidence and partly by the greater duration of the thyrotoxicosis in a masked form
(4) Pressure symptoms in the neck are much more likely to arise with toxic adenoma than with primary thyrotoxicosis and the explanation appears to be mechanical

To these four may perhaps be added a group of cases in which wasting is the predominant feature and the condition often considered to be that of malignant cachexia the underlying thyrotoxicosis being unsuspected

When we consider treatment there are certain differences of response compared with primary thyrotoxicosis Thus in toxic adenoma

(1) The response to iodine is less constant and of lesser degree
(2) The response to thiouracil is delayed possibly due to thyroglobulin already stored in vesicles and free for secre

tion and according to some observers ultimate results with thiouracil are qualitatively less satisfactory than in primary thyrotoxicosis

(3) The response to radiation is perhaps less satisfactory

(4) The tendency to recur after thyroidectomy is much less than in primary thyrotoxicosis again suggesting that the secretion of thyrotrophic hormone is not a factor

From a practical point of view I think that thyroidectomy is the best treatment for toxic adenomas especially as a small per centage may prove to be malignant I have however obtained quite satisfactory results with toxic adenomas by radiation and with thiouracil Both these latter forms of therapy are how ever contra indicated if pressure symptoms are already present as they may be dangerously exacerbated in the initial phase of treatment The response to radio active iodine by mouth is good but less constant than that met with in exophthalmic goitre and further the nodules may remain palpable even though the gland diminishes in size

CHAPTER XXIII

CARCINOMA OF THE THYROID

CARCINOMA of the thyroid is nearly always superimposed on a pre existing goitre of some years standing which is more commonly but by no means invariably nodular Its incidence is highest in areas of endemic goitre and for the Berne area has been as high as 1 04 per cent In non endemic areas it is more like 0 1 per cent and there is a preponderance among females as in non malignant thyroid disease Much higher values are given by some pathologists The malignant condition may occur at all ages but is usually after the age of 50 and more frequently in the late fifties or in the sixties

Pathology

Some 95 per cent of all malignant thyroid tumours are carcinomatous and of these 90 per cent originate in adenomas Sarcomas and endotheliomas are exceptional Occasionally the pathologist is unable to decide on histological grounds between adenoma and carcinoma even when the latter condition is made certain by the occurrence of multiple metastases

Clinical Features and Diagnosis

Joll pointed out that the following features indicate malignancy

(1) Rapid growth of the thyroid swelling
(2) Marked hardening of consistency
(3) Rapid development of severe thyrotoxic symptoms
(4) Fixation to surrounding structures of a nodular hard and irregular tumour
(5) Pressure symptoms dysphagia dyspnoea cough displacement of larynx paralysis of recurrent laryngeal nerve with or without vocal disturbance oedema of the head and neck from venous pressure pain from involvement of sensory nerves (It must be remembered that symptoms resulting from pressure on the trachea and *oesophagus* may occur with a simple adenomatous goitre but symptoms of any severity are unusual especially if they occur in the erect as well as the prone position)

Of thyroid tumours found to be malignant at operation some 30 per cent are unsuspected clinically and this seems to be a further reason for treating toxic adenomas of long standing surgically in preference to any other measures On the other hand lymphadenoid goitre (which see) may have the clinical features of malignancy and only be diagnosed at operation The thyroid like the breast prostrate and bronchus is one of these sites from which a small unsuspected and quiescent primary carcinoma may give rise to multiple metastases in bone skin and other organs these metastases being the presenting feature

Occasionally when the clinical features are those of a malignant thyroid the surgeon comes upon a rare inflammatory condition known as Riedel s disease The disease is characterized by the appearance in a normal or simple enlargement of the thyroid of a hard mass which later tends to invade the whole gland and eventually to spread into the surrounding structures such as the tracheatal walls carotid sheath and cervical muscles Joll states that its clinical features closely simulate slowly growing malignant diseases although pathologic illy it is undoubtedly an inflammatory condition in which fibrosis eventually dominates the picture It may occur at any age and the cause is unknown

Prognosis

Thirty per cent survive over 5 years if the carcinoma has not penetrated into surrounding tissue

Treatment

Radical surgery followed by deep radiation or a radium collar is the method advocated by Joll I have seen radio active iodine produce considerable amelioration but tracer studies show that some malignant thyroid growths and especially their metastases have little or no affinity for radio active iodine

CHAPTER XXIII

CARCINOMA OF THE THYROID

CARCINOMA of the thyroid is nearly always superimposed on a pre-existing goitre of some years' standing, which is more commonly, but by no means invariably, nodular. Its incidence is highest in areas of endemic goitre and for the Berne area has been as high as 1·04 per cent. In non-endemic areas it is more like 0·1 per cent., and there is a preponderance among females as in non-malignant thyroid disease. Much higher values are given by some pathologists. The malignant condition may occur at all ages, but is usually after the age of 50, and more frequently in the late fifties or in the sixties.

Pathology

Some 95 per cent. of all malignant thyroid tumours are carcinomatous and of these 90 per cent. originate in adenomas. Sarcomas and endotheliomas are exceptional. Occasionally the pathologist is unable to decide on histological grounds between adenoma and carcinoma even when the latter condition is made certain by the occurrence of multiple metastases.

Clinical Features and Diagnosis

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(3) Rapid development of severe thyrotoxic symptoms.

(4) Fixation to surrounding structures of a nodular, hard and irregular tumour.

(5) Pressure symptoms: dysphagia, dyspnoea, cough, displacement of larynx, paralysis of recurrent laryngeal nerve with or without vocal disturbance, oedema of the head and neck from venous pressure, pain from involvement of sensory nerves. (It must be remembered that symptoms resulting from pressure on the trachea and oesophagus may occur with a simple adenomatous goitre, but symptoms of any severity are unusual, especially if they occur in the erect as well as the prone position.)

In idiopathic malignant exophthalmos Brain and Turnbull showed that the thyroid gland was not typical of thyrotoxicosis and there was no constant pathological picture Turnbull states There is in short more evidence of colloid retention and less evidence of colloid secretion or transference than in goitres characteristic of Graves s disease the changes are not incompatible with Graves s disease but they correspond to findings that are unusual in Graves s disease and are of a kind that are only found in five out of a series of 50 glands

Incidence

The disease is most commonly found in middle age 80 per cent of Brain s original series being over 40 years of age whereas in Graves s disease the majority are under 40 In Brain s series the ratio of males to females was about equal whereas in Graves s disease there are nearly ten times as many women as men affected In the post thyroidectomy group Brain found four times as many males as females which considering the original incidence of thyrotoxicosis indicates a marked susceptibility of males to develop exophthalmic ophthalmoplegia

Clinical

There are three major groups

(1) In association with thyrotoxicosis
(2) After thyroidectomy
(3) Idiopathic i e in the absence of any evidence of severe disturbance of thyroid function

(1) *Thyrotoxic group* Severe exophthalmos may be associated with severe Graves s disease but rarely if ever with secondary thyrotoxicosis If it is sufficiently severe paralysis of movement of the eyes in one or more planes follows It is important to differentiate true exophthalmos from apparent exophthalmos caused by lid retraction (see Thyrotoxicosis section)

(2) *Post thyroidectomy group* Thyroidectomy for thyrotoxicosis if successful in restoring the metabolism to normal usually abolishes lid retraction but does not have the same fundamental effect on true exophthalmos although if the latter is not too far advanced there may be some amelioration In many patients however the exophthalmos is not influenced and in a

CHAPTER XXIV

MALIGNANT EXOPHTHALMOS

(*Exophthalmic Ophthalmoplegia*)

Definition

A CONDITION of severe exophthalmos associated with apparent paralysis of the extra ocular muscles of the orbit occurring in *the presence or absence of thyrotoxicosis* and not relieved by the abolition of thyrotoxicosis

Aetiology and Pathology

Thyrotrophic hormone can produce exophthalmos in guinea pigs &c in the absence of the thyroid gland (Smelser 1937) Such exophthalmos can also be produced by hypothalamic *stimulation by the use of cyanides* either in the absence of the thyroid gland or in the presence of the thyroid gland (Marine and Rosen 1934) In the latter circumstances the thyroid is hyperplastic but the metabolism is well below normal as in post operative myxoedema It is therefore quite certain that a form of exophthalmos is not due to thyroxine but to the secretion of thyrotrophic hormone or direct hypothalamic stimulation As regards the histology of the orbital muscles Brain who has differentiated the clinical syndrome (1936 and 1938) records the observations of Naffziger (1931) and Stallard (1936) and further studies by Turnbull (1938) The muscles are enlarged five or more times the normal size they are oedematous and show loss of muscle structure with fragmentation and destruction of muscle fibres fibrosis hyalinization and round celled infiltration The paralysis appears to be due to mechanical obstruction to movement in the much swollen contents of the orbit and to involve planes of movement rather than individual muscles Rundle and Pochin (1944) also note an increase in intra orbital fat and found no essential difference in the pathology of the orbital contents in malignant exophthalmos or in relatively mild exophthalmos associated with thyrotoxicosis

Brain has drawn attention to the frequency of shock or emotion in the production of malignant exophthalmos and Simpson (1945) has stressed the potential role of the hypothalamus



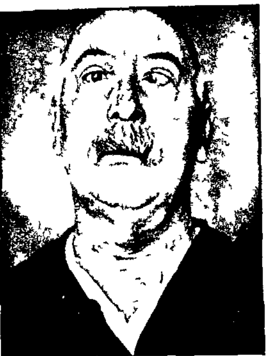


Fig. 51. Four cases illustrating exophthalmic ophthalmoplegia. Upper left shows haemorrhagic oedema of conjunctivae and ulceration of cornea; upper right shows paralysis of elevation; lower left associated with chronic thyrotoxic myopathy; lower right associated with pigmentation of face and neck. (By courtesy of Dr. W. Russell Brain, *Quart. J. Med.* (1938) vii, 6.)



Fig 1 Second case

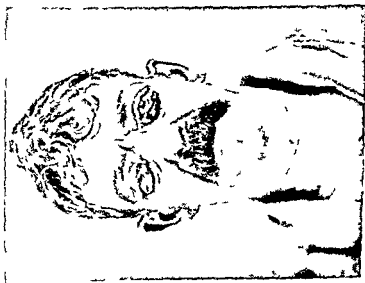


Fig 1 First case

of any hyperthyroidism that may be present Simpson (1945) suggested that the thyroid gland in these cases is relatively refractory to the thyrotrophic or hypothalamic stimulus Small light brown freckles and areas of cutaneous pigmentation on the face neck and hands were not uncommon

Course and Prognosis

In almost all cases the exophthalmos and ophthalmoplegia having reached their maximum in a few months either remain stationary or partially subside in either case leaving the patient with considerable disfigurement and double vision (Brain 1938)

Treatment

Apart from the good results of giving thyroid extract in appropriate dosage to those patients in whom the condition has followed too radical thyroidectomy with resulting hypothyroidism and low B M R the treatment of malignant exophthalmos is on the whole disappointing and often quite useless

Brain found deep radiation of the pituitary region to be unsuccessful and thyroidectomy for those patients with a raised B M R to be rarely beneficial The latter is not surprising if the primary stimulus is directly hypothalamic or thyrotrophic (Simpson 1945) Attempts to inhibit a pituitary thyrotrophic stimulus by oestradiol in women and testosterone in men are similarly not very effective The physiological inhibition of the secretion of thyrotrophic hormone is thyroid extract and that can only be given in large quantities if the basal metabolism is low and not raised The best treatment of malignant exophthalmos is probably prophylactic namely psychotherapy and barbiturates at the time of shock or emotional disturbance

Naffziger s operation consists of a decompression of the orbit after removal of its roof by a transfrontal approach The bulging of the orbital contents at operation indicates the great intraorbital tension However Professor Ida Mann regards the operation as obsolete In her series apart from the giving of thyroid she relied upon tarsorrhaphy and plastic operations on the lid and conjunctiva where necessary and obtained good results Direct radiation of the orbits may be beneficial

small percentage it becomes progressively worse This unfortunate result may be associated with a too radical thyroidectomy and a resulting myxoedematous condition with reduction of the basal metabolic rate to well below normal In another group the thyrotoxicosis persists in some degree, and in others the basal metabolism is neither raised nor lowered but the exophthalmos gets worse

(3) *Idiopathic group* There is frequently a history of shock or emotional stress The onset is acute or more usually subacute and one eye is often affected before the other and in different degree Exophthalmos may precede the ophthalmoplegia or both may develop simultaneously Diplopia is frequent The unequal degree of ophthalmoplegia often gives the appearance of a squint Brain found ophthalmoplegia unilateral in 13 patients and bilateral in 18 The ophthalmoplegia is a paresis or paralysis not of individual extra ocular muscles but of movement of the eye in a particular plane When the ophthalmoplegia is unilateral elevation is the movement most often affected The degree of weakness of an ocular movement is *usually constant from day to day and does not fluctuate though* a movement may gradually become weaker or further movements may become involved as the exophthalmos increases

The exophthalmos is always associated with some oedema of the loose tissues of the upper and lower lids and if there is much exophthalmos the oedema may be considerable In such cases there is also oedema of the conjunctiva which gives it an abnormally glistening appearance and causes it to be thrown into folds at the canthi when the patient moves the eye to either side In severe cases corneal anaesthesia and ulceration may occur Papilloedema and optic atrophy are rare complications

Of Brain s series of 31 cases the thyroid was visibly enlarged in 5 and appeared slightly enlarged on palpation in a further 9 Signs of mild hyperthyroidism were not uncommon but corresponding symptoms were rarely complained of and the patient s placid appearance in spite of the exophthalmos was in striking contrast with the anxious expression of the typical patient with exophthalmic goitre In 8 patients in whom basal metabolism was investigated the average increase was plus 25 per cent However there is a very obvious discrepancy between the severity of the exophthalmic ophthalmoplegia and the mildness

CHAPTER XXXI

MENOPAUSAL HYPERTHYROIDISM

Both primary and secondary thyrotoxicosis may first appear at the menopause In both cases the stimulus appears to be the pituitary thyrotropic hormone since other evidence of pituitary hyperfunction secondary to the physiological castration of this period is available Oestrone though abolishing other manifestations of pituitary over activity does not appear to be of appreciable help in diminishing the severity of climacteric thyrotoxicosis Fundamentally the appropriate treatment is that of idiopathic forms of thyrotoxicosis (which see)

CHAPTER XXV

PUBERTY GOITRE

A SLIGHT or moderate diffuse enlargement of the thyroid frequently occurs at puberty with slight or no symptoms This condition should be regarded as physiological since it may disappear entirely after some years or may be obvious only during menstruation But the thyroid may enlarge considerably and thyrotoxicosis may supervene

The thyroid is sometimes very large at puberty without any symptoms It is then often called a colloid goitre but this term may be misleading and assumes a pathological condition not constantly present Symptoms of thyrotoxicosis may develop later

Enlargement of the thyroid at puberty is probably due to relative deficiency of iodine associated with the temporarily increased demands of the body Small doses of iodine or of thyroid gland may cause involution of the gland or prevent enlargement These measures which are by no means always successful are sometimes wrongly blamed for apparently causing the onset of secondary thyrotoxicosis

(c) Clinical

The enlargement may be present at birth or in early childhood but may not arise until puberty when there is an additional demand for thyroid function or it may not be observed until adult life The relationship of the simple diffuse colloid goitre of puberty which may spontaneously disappear to that of the more characteristic multilobular endemic goitre in adults is not certain but there is a high incidence of such puberty goitres in endemic goitre zones Such puberty goitres therefore are probably an expression of iodine deficiency aggravated by peaks of physiological demand for thyroxine Occasionally goitres may not be observed until the climacteric when initial or further enlargement occurs At all ages the incidence is much higher in women

In the majority of cases in this country there is no gross disturbance of thyroid function but mild degrees of hypothyroidism as well as characteristic myxoedema are met with and secondary thyrotoxicosis may supervene on a symptomless goitre especially at the climacteric phase Endemic cretinism was once common in parts of Switzerland but not in this country

If the goitre is multilobular and large pressure symptoms in the neck may be troublesome even with non malignant goitres and in a small percentage of cases malignancy supervenes

(d) Aetiology

In 1852 Chatin observed that in certain areas of the Alps the food soil and water were deficient in iodine and even suggested that iodine might be of use prophylactically Wagner-Jauress of Vienna in 1898 recommended the general introduction of iodine in salt as a prophylactic measure against goitre in endemic goitre areas Theodore Kocher of Berne believed that there was a goitre producing substance in the water and that it could be destroyed by boiling McCarrison in India showed that on that continent there was not an absolute deficiency of iodine but that water contamination and/or vitamin deficiency could produce endemic goitre

Nevertheless the iodine deficiency (relative or absolute) theory

CHAPTER XXVII

ENDEMIC GOITRE

(a) Incidence

GOITRES or thyroid enlargements may occur in a high percentage of the population children and adults in many geographical areas throughout the world In parts of Switzerland the incidence was as high as 90 per cent before the prophylactic use of iodine

It is perhaps not generally realized that the goitre problem in Great Britain and Ireland is a serious one Thus the Goitre Sub Committee of the Medical Research Council state that in England and Wales at the present time it is estimated that there are some 500 000 cases of thyroid enlargement in persons of ages 5 to 20 inclusive In Oxfordshire goitre is present in 37 per cent of girls in the Isle of Wight 36 per cent in Durham 34 per cent in Somerset 28 per cent and in Devon and Cornwall 18 per cent The incidence among boys is about 30 per cent of that among girls The Medical Research Council in Ireland reported that in the South Riding of Tipperary 50 per cent of the children were goitrous and at the Cashel Industrial School 90 per cent In 1901 Sir James Berry drew attention to the high incidence of goitre in South Wales particularly in Glamorganshire

There are many areas in the American continent where goitre is endemic

(b) Pathology

According to the physiological phase (and past phases) at the time of section areas of hyperplasia colloid involution or adenomatous formation may predominate or occur in different portions of the gland The distribution of such areas has been attributed to variability of the blood and lymphatic supply Exhaustion atrophy (associated with cretinism and myxoedema) is also a terminal sequence microscopic examination reveals desquamation and degeneration of the lining cuboidal cells with fragmentation and irregular staining of the nuclei a loss of colloid material and an increase of fibrous stroma

by even smaller quantities e g given as sodium iodide 1 200 000 mixed with salt a total of 18 mg of sodium iodide in a year may be adequate Iodine is also given as a chocolate coated tablet containing $\frac{1}{6}$ grain (10 mg) one being given weekly for a year before puberty and two years afterwards The giving of iodine in small quantities to pregnant women with goitre will prevent congenital goitres in the same way as it will prevent goitres appearing in the puppies of thyroidectomized dogs

The Medical Research Council in Great Britain has drawn attention to the increased incidence of endemic goitre in 1917–18 as well as in 1943–4 when there has been a deficiency of fish and other iodine containing sea foods But apart from the securing of appropriate diets in general and especially in endemic goitre areas they strongly recommend that iodized salt containing 1 part of potassium iodide in 100 000 parts of salt should be generally available With an average daily intake of 10 gm of salt per person this would provide 0 1 mg of iodide or 0 08 mg of iodine They state that no ill effects are to be expected from the widespread use of iodine in such concentrations—indeed the bulk of the evidence is to the contrary and advise an official pronouncement in favour of its general employment This seems to be advisable on general grounds considering *the population as a whole But some clinical observers have* thought that in a small percentage of cases of symptomless adenomatous goitres especially in middle aged women the giving of small quantities of iodine has been followed by the development of thyrotoxicosis Bauer has recently pointed out that after Wiesel and Kretz called attention to the apparent harm caused by the general sale of iodized salt in Austria the order was given to sell pure salt generally and iodized salt only on demand Quite apart from iodine however the natural history of endemic goitre may be the supervention of thyrotoxicosis in some cases of hitherto symptomless goitre and Davies and Rogers found a high incidence of toxic adenomatous goitre in areas of endemic goitre in Wales There certainly appears a good case for the general use of iodized salt from childhood as a sound prophylactic measure

(f) Treatment

If prophylaxis has failed small doses of iodine such as

seems to offer the simplest and most consistent explanation of endemic goitre and has *the following facts to support it*

(1) the soil and water usually have a low iodine content
(2) the blood has a subnormal iodine content
(3) *the incidence of goitre has been reduced from 90 to 10 per* cent by the prophylactic use of small quantities of iodine (e g in Zurich)

Against the iodine deficiency theory is the fact that in some endemic areas the iodine content of the water and soil is normal A relative iodine deficiency may however be produced by com*plicating factors (a) an infective element (contaminated water)* (*b*) a high calcium content of the water (*c*) a goitrogenous substance e g cabbage and methylcyanide (*d*) a vitamin deficiency *An increased physiological demand for iodine e g* puberty pregnancy and menopause may reveal or aggravate a geographical iodine deficiency

According to Marine a relative or absolute iodine deficiency results in thyroid hyperplasia (possibly via the pituitary thyrotropic hormone) If the iodine deficiency is temporarily abolished by an increased supply of iodine or a diminution of physiological demand the gland (or a portion of it) involutes to the colloid resting phase A further iodine deficiency produces hyperplasia and a sequence of phases of hyperplasia and involution produce adenomas (which later may become autonomous and even malignant) Ultimately exhaustion atrophy may result

The hyperplasia is usually ineffectual in that thyroid function is still subnormal This is because a hyperplastic gland cannot make an excess of thyroxin in the absence of inadequate supplies of iodine Given iodine normal function may result Very occasionally however *the hyperplasia not only persists but leads* to an effective hyperfunction Thus hyperthyroidism may be an untoward result of treating a symptomless (or myxoedematous) *adenomatous goitre with an excess of iodine* (Iodine-Basedow) The problems of endemic goitre are best understood by attempting to apply what is already known about the physiology and mechanism of the normal thyroid and of other forms of goitre

(e) Prophylaxis

It is said that the normal requirements of the body are 0 04 to 1 mg of iodine per day *and successful prophylaxis is achieved*

CHAPTER XXVIII

MYXOEDEMA

Definition

Myxoedema is a condition of hypothyroidism occurring sporadically often in middle aged women it is also associated with endemic goitre and is occasionally a sequel to hyperthyroidism Myxoedema usually occurs in adults more frequently women but may occur in childhood Juvenile myxoedema is a term applied to myxoedema commencing in childhood but not present at birth the latter being termed cretinism

The term myxoedema is not applicable to hypothyroidism secondary to anterior pituitary deficiency as occurs in Simmonds s disease In myxoedema the essential pathology is in the thyroid gland itself and its subnormal function cannot be increased by injections of thyrotrophic hormone

Historical

Hilton Fagge physician to Guy s Hospital who first described sporadic cretinism predicted in 1871 that a similar condition would be found sporadically in adult life Though his senior colleague W W Gull reported five such cases in 1873 J B Bramwell had already described the same condition in 1869 but had not published his account The term myxoedema was suggested by W M Ord of St Thomas s Hospital in 1877 because of the excess of mucin found in the skin Myxoedema was ascribed to thyroid deficiency in 1883 by Felix Semon who also concluded that cretinism and post thyroidectomy myxoedema (cachexia strumipriva) were both due to the same cause In 1891 G R Murray of Manchester successfully treated myxoedema by injections of a glycerin extract of sheep s thyroid and in the following year Hector Mackenzie and E L Fox independently reported successful therapy with dried thyroid gland administered orally

Aetiology

The disease has a predilection for multipara and a special incidence at the climacteric when involution and fibrosis of

3 minims of Lugol's iodine daily may assist the involution of goitre when adolescent or pubertal Small doses of dried thyroid which also of course contains iodine are sometimes used *Surgical interference during adolescence is inadvisable since* recurrence with resultant myxoedema is frequent Small doses of iodine can also be used when the gland is enlarged in pregnancy or at the climacteric The danger of iodine resulting in hyperthyroidism in long standing cases especially with obvious irregularity (adenomas) of the goitre appears to be slight Surgery is necessary for pressure symptoms or to satisfy aesthetic demands Thyroid is indicated for myxoedema or cretinism

myxoedema must be regarded as secondary to the primary thyroid deficiency

As myxoedema may occur at any age including childhood one might postulate that it also results from a general infection (compare the effect of mumps on the gonads) but there is rarely any clinical evidence of this probably because of the long latent period However a condition known as acute thyroiditis does occur although rarely in the course of scarlet fever measles mumps acute rheumatism typhoid fever and puerperal fever The thyroid gland is swollen and painful and sometimes suppuration and abscess formation occur A follow up of such cases has not been undertaken

Lymphadenoid goitre which usually occurs in women over 40 and in which there is an extensive lymphoid infiltration of the thyroid gland is sooner or later associated with myxoedema If partial thyroidectomy is undertaken for pressure symptoms myxoedema almost invariably follows or is exacerbated if previously existing The condition however is very rare and then diagnosed only at operation

Myxoedema may spontaneously follow thyrotoxicosis which has been expectantly treated over a number of years possibly by exhaustion of the thyroid gland although Zondek reported one case which passed from thyrotoxicosis to myxoedema and then (following pregnancy) to thyrotoxicosis again Some degree of myxoedema occurs in a small percentage of cases of thyrotoxicosis treated by thyroidectomy deep radiation or thiouracil In the treatment of cardiac disease by complete thyroidectomy myxoedema is intentionally produced to diminish the work of the heart

Perhaps the majority of cases of myxoedema occur in geographical zones of endemic goitre which has been considered under that heading

Pathology

Apart from endemic goitre (which see) the thyroid gland in idiopathic myxoedema has undergone fibrosis and atrophy The skin and subcutaneous tissues are infiltrated with mucoid material containing nitrogen The heart muscle may be similarly affected and show myocardial degeneration Degeneration of the coronary arteries is sometimes a complication or concomitant

other endocrine glands e g the ovary may occur The condition is not due to deficient secretion of thyrotrophic hormone



FIG 5? MYXOEDEMA FOLLOWING THIOURACIL Puffy eye B M R minus 26 per cent Pulse 50 Hypersensitivity to cold loss of hair from the outer eyebrows (Unfortunately no photograph was taken before treatment but typical Graves s disease with lid retraction and some exophthalmos) Patient continued 400 mg of thiouracil daily for months without control observations

as there is an excess of this hormone in the blood in myxoedema (just as there is an excess of gonadotrophic hormone at the climacteric) and injected thyrotrophic hormone is without effect Complete thyroidectomy results in excessive secretion of pituitary thyrotrophic hormone so that the latter phenomenon in

trast to Simmonds s cachexia where the pubic and axillary hair disappears The nails are striated and tend to break The soft tissues of the hands and fingers become thick and puffy and the muscles and ligaments become hypotonic flat feet being not uncommon The shoulders become rounded and the



FIG 53 MYXOEDEMA Woman of 6 who developed thyrotoxico is thirty years ago following the birth of h r so i the condition being treated med cally and gradually passing nto myxoedema as manifested by lo s of outer half of eyeb ow thick dry skin consid rable thinning of hair of head (t ansformat n worn) and great sen itivity to cold a r sidual exophthalmos mainly unilateral

abdominal walls flaccid and protuberant Apart from the mucoid infiltration there may be some increase of fat e g in the supra clavicular and suprapubic areas and above the wrists and ankles Adiposity is not however an essential of hypothyroidism

In contrast to hyperthyroidism appetite and thirst are subnormal and constipation is a constant feature Achlorhydria is frequent Menorrhagia is not infrequent Occasionally amenor rhoea is found

Cardiovascular system Although pathological changes in the heart muscle and even of the coronary vessels are not uncom mon in myxoedema cardiac symptoms are unusual However

In lymphadenoid goitre there is a widespread infiltration of the thyroid tissue with lymphocytes and little if any normal thyroid tissue remains Fibrosis occurs in the later stages

In acute thyroiditis there is a diffuse leucocyte infiltration of the gland with proliferation degeneration and desquamation of epithelial cells There may be haemorrhagic foci infarcts and abscess formation

Clinical Picture

The symptoms are the opposite of hyperthyroidism The onset is insidious the patient becoming lethargic apathetic and somnolent with a marked slowing of speech and intellectual processes and a failing of memory The condition is half way towards hibernation a low basal metabolic rate e g —40 with subnormal temperature and sensitivity to cold being the basis (as was shown by Magnus-Levy in 1896)

There is also a mucoid infiltration of the skin subcutaneous tissue tongue laryngeal mucous membrane heart and sometimes the liver producing a number of characteristic features The nose and lips tend to become thick and less well delineated but not comparable to the gross deformity of acromegaly Both lids are oedematous and the eyes may appear slit like in the midst of a puffy orbit Exophthalmos is usually absent in idiopathic myxoedema but may be present by itself or with ophthalmoplegia if myxoedema supervenes upon thyrotoxicosis e g after thyroidectomy The enlarged tongue may interfere with articulation or the laryngeal changes result in a hoarse husky or toneless voice The speech in any case is slow and sluggish, but this is probably due to retardation of the intellectual processes Impairment of smell taste and hearing may be present Even with a normal blood count the facial appearance is pallid due to the infiltration of the skin and a malar flush on the pallid countenance may be present Carotinaemia and a yellow colour of the skin is sometimes met with and multiple cutaneous xanthomata have been recorded The hair of the head is dry and lustreless and falls out This is also true of the eyebrows especially of the outer half and Holbein s portrait of Henry VIII by virtue of the scanty eyebrows and puffy face has been said to indicate myxoedema The pubic and axillary hair may become more scanty than usual but is usually retained, in con

responds neither to iron nor liver, but to thyroid gland (although slowly) which is therefore presumably due directly to the hypothyroidism Bomford describes the condition thus

This simple hyperchromic anaemia is never severe the colour index is normal or a little above one There is some macrocytosis but no poikilocytosis and no excessive anisocytosis The reticulocyte count may be normal or a little above normal The gastric function may be normal or there may be achlorhydria The administration of liver or of iron has no effect on the anaemia but the anaemia does respond slowly to treatment with thyroid alone in such doses as are found to keep the patient free from symptoms of myxoedema or over dosage The rate of response is very slow the blood count attaining normal levels in from three to nine months

He regards the anaemia as a result of a decrease in the size of the erythron which takes place in hypothyroidism as a physiologic compensation for diminished need of the tissues for oxygen and akin to the anaemia which appears in animals exposed to atmospheres of oxygen tension greater than normal The bone marrow is hypoplastic and sternal puncture shows a reduction of nucleated cells The serum bilirubin is normal Glass reported a similar macrocytic anaemia which required testosterone in addition to thyroid before the blood picture reverted to normal Leucopenia and relative or absolute lymphocytosis is not infrequent and eosinophilia may be found occasionally

Generative organs In thyrotoxicosis one often meets with amenorrhoea or oligomenorrhoea and in myxoedema menorrhagia occurs Many text books state that amenorrhoea is the most frequent finding in myxoedema but I believe this to be quite incorrect and due to confusion of myxoedema with hypothyroidism secondary to hypopituitarism In the latter condition amenorrhoea is the rule but in myxoedema an excessive and irregular menstrual bleeding is not infrequent Gynaecologists even give thyroid extract empirically for menorrhagia in the absence of clinical myxoedema and claim good results In juvenile or childhood myxoedema however there is often retardation in sexual development and in the onset of menstruation unless the condition has been treated with thyroid Of course if myxoedema occurs at the climacteric there will be associated amenorrhoea but this may be preceded by menorrhagia

Emotional pattern and psychoses Sluggish mental reactions poor memory slow speech absence of emotional response and

cardiac failure may occasionally occur and anginal pains are sometimes a manifestation of myxoedema The pulse rate is nearly always slow but may become quick if cardiac failure supervenes Coronary degeneration and hypertension may be concomitants rather than complications in older patients as may also angina as myxoedema does not necessarily protect people against arteriosclerotic or other degenerative vascular changes Since however myxoedema following thyroidectomy ameliorates cardiac pain and insufficiency it follows that manifestations of these features in spontaneous myxoedema may indicate a greater degree of pathological disturbance than in normal people This is also suggested by the fact that whereas cardiac symptoms are comparatively rare in spontaneous myxoedema radiological and electrocardiographic abnormalities are comparatively common Thus cardiac enlargement as revealed by X ray examination is found in more than 50 per cent of patients It is usually associated with myxoedematous infiltration of the cardiac muscle and the condition tends to return to normal on giving thyroid by mouth There may be a pericardial effusion as well The electrocardiogram reveals diminution in the size of all the waves the QRS complex is of low voltage and the T waves are flat or inverted Under treatment the P and QRS waves become larger and the T waves become upright Zondek has pointed out that the capillaries in myxoedema are usually very narrow and that only the loops of the capillaries may be visible the limbs being invisible unless substitution thyroid therapy has reversed these abnormalities There is slurring of the capillary circulation

Gastro intestinal In contrast to hyperthyroidism appetite and thirst are subnormal and constipation is a constant feature Intestinal movements are often sluggish and intestinal absorption slow Achlorhydria is frequently shown by a fractional test meal The liver may be enlarged and palpable probably due to mucinous infiltration and recedes to normal size on thyroid therapy

Blood picture Possibly associated with the achlorhydria a simple hypochromic microcytic anaemia responding to iron or a typical Addisonian megalocytic hyperchromic anaemia responding to liver may occasionally be found associated with myxoedema There is however a third type of anaemia which

also diminished compared with normal and a positive balance existed Thus per 3 day period there was a retention of phosphorus amounting to 4 21 mg per kg body weight compared



FIG 54 MYXOEDEMA Woman aged 59 showing loss of hair from scalp and eyebrows and enormous distended abdomen referred to hospital as intestinal obstruction died in a torpor autopsy revealed complete atrophy of the thyroid gigantic hypertrophy of the colon with myxoedematous infiltration (By courtesy of Dr Paul Bastenie Brussels *Lancet* 1946 i 413)

with a loss or negative balance in normal subjects of 10 5 mg Thyroid extract produced an approximation to normal Examination of the blood in myxoedema showed that the calcium and inorganic phosphorus of the serum are normal but that the serum phosphatase is diminished There is no clinical pathological or radiological evidence of increased density of the bones or increased calcium deposition in myxoedema in contrast

general inertia are characteristic Neurosis is rare but psychosis common enough in untreated cases to justify the psychiatrist being aware of myxoedema as a possible cause of a psychosis The latter may be delusional or hallucinatory or schizophrenoid In early cases there is a good response to thyroid therapy

Metabolic and biochemical changes (1) Basal metabolism is invariably low usually in the neighbourhood of minus 40 per cent (2) Blood cholesterol is usually raised and sometimes very considerably Normal values for blood cholesterol average 160 mg per cent and any value above 250 mg per cent suggests myxoedema It is rare to find values above 500 mg per cent but values as high as 953 mg per cent have been recorded even when the basal metabolism was no lower than minus 38 per cent There is usually some relationship between basal metabolism and cholesterol but it is by no means constant and some observers attach greater importance to blood cholesterol than to basal metabolism as a measure of the presence or severity of myxoedema Occasionally xanthomatous nodules occur on the face and along the extremities and in one such case the serum was of a milky character as in lipaemia There was only a tardy and partial response to thyroid therapy and the condition is so infrequent as to be regarded as coincidental rather than as part of the myxoedematous syndrome Nevertheless thyroidectomy in the dog produces a high level of blood lipoids as well as cholesterolaemia (3) *Renal function* Although water excretion is normal in myxoedema Beaumont and Robertson have shown that renal function is impaired as shown by the urea clearance test and that although this is improved by thyroid therapy it may remain slightly subnormal Thyroid administration in normal people as in myxoedema however produces a water diuresis and a lowering of the specific gravity of the urine Robertson suggests that in myxoedema the renal threshold for calcium is raised (and in thyrotoxicosis lowered) and that this is a possible explanation of the changes in calcium and phosphorus metabolism described below (4) *Calcium and phosphorus studies* In three cases of myxoedema Robertson found that the negative calcium balance was less than normal i e 4 78 mg per kg of body weight per 3 day period compared with the normal of 7 58 mg and that the diminution of calcium output chiefly affected the urine The phosphorus output was

the association of localized myxoedema with generalized thyrotoxicosis and based on the fact that in one patient the condition appeared after thyroidectomy at the same time as exophthalmos became severe led to the postulation of the pituitary thyrotrophic hormone as being an aetiological factor Clinically the lesions appear on the anterior lateral aspect of the legs commencing in the lower half and are usually bilateral The skin is raised in irregular firm swellings the uneven contours of which are the most characteristic feature of the condition The swellings are in the skin rather than beneath it for the skin cannot be moved independently The attachment of hair follicles to deeper structures often produces a characteristic dimpled or pig skin appearance The skin is commonly a faint pink or sometimes brown colour and the growth of numerous coarse hairs from the affected skin is a marked feature of some cases Microscopically the connective tissue fibres of the cutis are split apart by a substance staining pink with thionin blue a reaction specific for mucin Carol extracted a mucin like substance chemically which after hydrolysis with weak acid reduced Fehling s solution

The response to thyroid extract is not unexpectedly poor or absent but in some patients a spontaneous amelioration of the condition occurs over a number of years and occasionally it disappears entirely

Diagnosis

Clinical diagnosis is suggested by loss of hair of the head loss of outer half of eyebrows loss of memory and sluggish mental reactions and speech hypersensitivity to cold puffy eyelids pallor and bradycardia Low basal metabolic rate and high blood cholesterol values are confirmatory evidence It is probably true that relatively mild degrees of myxoedema are missed clinically but in my experience sporadic well developed myxoedema is a rare condition I believe it to be more rare even than the rare condition of Simmonds s disease which syndrome is not infrequently labelled myxoedema because of the secondary hypothyroidism Amenorrhoea and absent pubic and axillary hair favour the diagnosis of Simmonds s disease especially when the symptoms have commenced after parturition The response of Simmonds s disease to thyroid therapy is inadequate

with the osteoporosis of thyrotoxicosis (5) *Carbohydrate metabolism* Some observers claim an increased tolerance of carbohydrate in myxoedema and the glucose tolerance curve may be subnormal in height The relatively small increase in blood sugar values after glucose is probably due however to the delayed rate of intestinal absorption Fasting blood sugar values are usually normal in contrast to the fasting low blood sugar values in hypothyroidism secondary to pituitary insufficiency (Simmonds s disease)

Biochemical Investigations

The blood cholesterol (normal 160–190) which is invariably raised and often considerably so e g 500 mg per 100 c c is a valuable indication of the extent of the condition and its subsequent course under therapy The blood sugar may be low and the carbohydrate tolerance increased but the opposites also occur

Juvenile Myxoedema

This condition is rare and by definition refers to the condition of myxoedema commencing in childhood but not present at birth as in cretinism The symptoms are those of myxoedema but in addition there is deficient growth delay in the appearance of the centres of ossification delayed sexual maturity and mental deficiency The cause is believed to be some acute infection in childhood e g measles but nothing certain is known about this Early treatment will produce a return to normality

Localized Myxoedema

There are two types (*a*) Local areas of excessive deposition of mucin in the skin and subcutaneous tissues scattered irregularly over the face body and limbs and almost invariably associated with generalized myxoedema The areas are macular papular and lichenoid The condition is rare (*b*) The condition of localized pretibial myxoedema which is generally associated with some degree of thyrotoxicosis but may occur with myxoedema Trotter and Eden (1942) reviewed 73 cases from the literature and added 4 of their own Thirty five of the cases occurred after thyroidectomy but in most of these there was a residual degree of thyrotoxicosis It is very difficult to explain

the association of localized myxoedema with generalized thyrotoxicosis and based on the fact that in one patient the condition appeared after thyroidectomy at the same time as exophthalmos became severe led to the postulation of the pituitary thyrotrophic hormone as being an aetiological factor Clinically the lesions appear on the anterior lateral aspect of the legs commencing in the lower half and are usually bilateral The skin is raised in irregular firm swellings the uneven contours of which are the most characteristic feature of the condition The swellings are in the skin rather than beneath it for the skin cannot be moved independently The attachment of hair follicles to deeper structures often produces a characteristic dimpled or pig skin appearance The skin is commonly a faint pink or sometimes brown colour and the growth of numerous coarse hairs from the affected skin is a marked feature of some cases Microscopically the connective tissue fibres of the cutis are split apart by a substance staining pink with thionin blue a reaction specific for mucin Carol extracted a mucin like substance chemically which after hydrolysis with weak acid reduced Fehling s solution

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and sometimes the condition is aggravated in contrast to the most gratifying response of myxoedema A low fasting blood sugar is usual in Simmonds s cachexia whereas it is uncommon in myxoedema In Simmonds s disease thyroid function and a normal metabolism is restored by injections of pituitary thyrotrophic hormone but in myxoedema the latter is completely without effect In both myxoedema and Simmonds s disease the daily excretion of 17 ketosteroids in the urine is very low below 2 mg and often below 0 5 mg

Course and Prognosis

Mild cases may remain stationary and undetected for years but others progress downhill unless treated The response to thyroid therapy is excellent

Treatment

This is a most satisfactory branch of endocrine therapy Dried thyroid gland should be given by mouth commencing with 1 grain daily and gradually increasing until the symptoms disappear Three grains daily is usually adequate but some patients may need much larger doses The pulse which should never be allowed to exceed 80 per minute is a good criterion of over dosage the basal metabolic rate and blood cholesterol are more exact criteria for controlling dosage It should be remembered that thyroid takes at least 24 hours to take effect and a few days to attain the maximum which (for a single dose) lasts 2 weeks and then gradually declines Thyroid need only be given therefore once a day any increase in dosage should be gradual a watch being kept for cumulative effects Too rapid a strain on the heart (possibly dilated already) may precipitate heart failure or induce angina It should be remembered that if complete thyroidectomy is used to relieve chronic heart failure the subsequent treatment of the post operative myxoedema aims at a judicious balance between relieving the latter symptoms partially and avoiding the strain from which the heart has been relieved by operation The latter procedure incidentally has been discarded in some endocrine-cardiac clinics as being impractical

Trotter and Wallace record a case of myxoedema in which thyroid by mouth produced vomiting They found that 7 5 mg

of thyroxine given intravenously increased a basal metabolism of minus 30 per cent to normal within 1 week and that during the next 3 weeks it gradually fell to minus 30 per cent again Ten milligrams of thyroxine however produced pains in all the limbs palpitation and diarrhoea the day after it was given intravenously and these untoward symptoms lasted 3 days Finally it was found that 7 5 mg thyroxine given intravenously at intervals of 4 weeks maintained the patient in good condition This is an average of less than 0 3 mg thyroxine daily

Anaemia both microcytic and macrocytic usually responds to iron and liver respectively In some cases however response is inadequate until thyroid is also given but thyroid should not be withheld except under experimental conditions Thyroid alone is often effective but the blood picture may take a long time to return to normal

CHAPTER XXIX

CRETINISM

Definition

This is a condition of hypothyroidism beginning in foetal life In contrast childhood myxoedema is superimposed on a normal infancy and early childhood

Aetiology

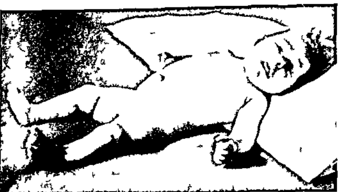
The endemic form occurs in goitrous areas the mother usually having a goitre The infant may be born with a goitre or the latter may develop after a few years Cretinism is common in some goitrous areas but rare in others The sporadic form is quite rare and may be due to a congenital absence of the gland or to a foetal infection (thyroiditis) leaving the gland fibrotic and atrophic The sex incidence is about equal

Symptomatology

This resembles that of myxoedema (q v) as both are due to hypothyroidism Special characteristic features are the broad nose with flat bridge and wide nostrils thick lips open mouth and protruding thick tongue protuberant abdomen with umbilical hernia supraclavicular pads of fat and spade like hands

Symptoms in the infant may not be observed for some months and then only when the retarded state of development is obvious The fontanelles remain open both primary and secondary dentition are delayed and the teeth become carious soon after eruption The centres of ossification appear late and the epiphyses often remain open unduly long In spite of this it is rare for an untreated cretin to reach a height greater *than 4 feet* This dwarfism may be due to a secondary diminution of eosinophil cells in the pituitary gland as has been sometimes noted

Deaf mutism is common The deafness may be due to swelling of the mucous membrane of the Eustachian tube The dumbness may be due to disproportionate size of the tongue and mental deficiency Some degree of the latter is almost constant The general attitude is one of apathy and sleepiness is common in the untreated state the cretin leads a vegetative



(a)



(b)

Fig 55 Cretinism (a) Untreated aged 18 months showing umbilical hernia open mouth and protruding tongue depression of nose absence of the outer half of the eyebrows thick skin puffy eyes cold blue hands and feet forehead was furrowed (unfortunately this is not clearly shown in the picture) (b) Treated with thyroid aged 2 years 3 months

existence Sexual development is retarded, and maturity may never be reached

Wilkins and Fleischmann (1944) record

We have seen one cretin who was entirely untreated until the age of 24 Her breasts had begun to develop at 16 to 17 years and pubic hair appeared at 22 years at which time she menstruated about once every six months At 24 years her breasts were fairly prominent There was a sparse growth of pubic hair The uterus and ovaries were about two thirds the normal size and biopsy showed a non secretory type of endometrium Another untreated cretin of 18 years had one menstruation at 7 and then menorrhagia at intervals of months from a proliferative endothelium

Treatment

Administration of thyroid extract in the early stages may result in the attainment of an approximately normal childhood and adult state If treatment has been delayed for some years the only result may be the conversion of a harmless apathetic idiot into a mischievous truculent and troublesome semi idiot Nevertheless excellent results are sometimes obtained when treatment is late and conversely early and adequate treatment may be disappointing

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SECTION FOUR

THE PARATHYROIDS

A PHYSIOLOGY

CHAPTER XXX

INTRODUCTION

In man and most animals there are four parathyroid glands embedded in the posterior substance of the thyroid gland two superior (or internal) and two inferior In the rat there are only two parathyroid glands and they are easily removed In adult man each parathyroid gland weighs about 50 mg and measures 6 × 4 × 2 mm Embryologically they arise as paired structures from the endoderm of the third and fourth branchial clefts Three types of cells may be found in parathyroid parenchyma (1) clear chief cells with non granular faintly staining protoplasm and large pale nuclei—the chief cells are the most numerous (2) very large *pyknotic* oxyphil cells with rich granular protoplasm taking up acid or eosinophil dyes and small deeply staining nuclei and (3) small dark cells with fine eosin granules and small nuclei—which cells may be the precursor of the large oxyphil cells The respective functions of these cells are not known and parathyroid adenomas may consist of any or all of these types of cell

EFFECT OF COMPLETE PARATHYROIDECTOMY

Before the parathyroids were discovered and separated from the thyroid gland (Sandstrom 1880 Gley 1891 and Kohn 1895—the last named *discovering the less obvious superior* or internal parathyroids) Schiff in dogs cats and rats (1859 and 1884) and Sir Victor Horsley (1885) in monkeys had observed that complete thyroidectomy might lead to acute nervous symptoms and death After Kohn s discovery *Vassalo and Generali* (1900) were able to remove the parathyroids of cats and dogs without removing the thyroid and to observe that parathyroidectomy led to death within 5 to 10 days with symptoms of hyper excitability tetany tachycardia vomiting and prostration The first fundamental biochemical approach

was that of MacCallum and Voegtlin (1909) who showed that parathyroidectomy led to a fall in serum calcium although later studies indicated that the primary action was a rise in serum phosphorus due to its decreased urinary excretion

The experimentally parathyroidectomized animal does not necessarily manifest clinical tetany as seen in man but may do so Fibrillary twitches occur in the muscles of the head face back and tail and may proceed to clonic contractures Extensor spasms of the limbs are frequent in dogs Epileptiform convulsions may occur Spasms also affect the larynx dia phragm cardiac and gastro intestinal musculature Vomiting and bloody diarrhoea is met with also severe hyperpyrexia (Simpson 1922) Food and water is refused Salivation sneezing and frantic scratching are further symptoms Occa sionally in contrast to the more usual hyper excitability the animals may be depressed and sluggish and may die of cachexia without symptoms of tetany The nervous hyper irritability (spasms and tremors) is peripheral and abolished by curare but toxic and clonic convulsions appear to be abolished by decerebration and are thought to be of cerebellar or mid brain origin This hyper irritability of nervous tissue is now proved to be due to a deficiency of ionized calcium concentration and abolished by its correction The older theory of an accumulation of toxic substances e g guanidine as the responsible mechan ism has been abandoned (Shelling 1935)

BIOCHEMISTRY OF TETANY

The normal concentration of total calcium in the serum is 9 to 11 mg per cent and in tetany due to hypoparathyroidism subnormal values e g 4 to 6 mg may be found Since however in other forms of tetany e g following intractable vomiting the total calcium concentration in serum may be normal it became necessary to study the different physico chemical forms in which calcium exists in the serum There are several ways of partitioning total calcium e g diffusible or non diffusible according to its passage through a suitable membrane These are present in about equal proportions The non diffusible is thought to be in some combination with serum protein possibly as a calcium proteinate (Shelling 1935) The diffusible portion may be adsorbable in mordants such as barium sulphate or not

The non adsorbable portion may be ionizable or not There is as yet no direct method of measuring ionizable calcium on a suitable electrode but there are several indirect methods e g the portion that is *instantly* precipitated by oxalate added to an ultrafiltrate of serum or the effect of a solution on the amplitude of a beat of the frog s heart This and other more physical methods are not beyond criticism and do not give constant results the latter varying between 2 to 5 mg per cent calcium concentration in normal serum There is however abundant evidence that tetany is dependent upon a subnormal concentration of ionized calcium regardless of the total calcium although a subnormal total calcium concentration almost invariably indicates a subtotal concentration of ionized calcium Although the serum calcium of normal mammals is constant within narrow limits this is not true of birds or fish where the serum calcium in the laying or breeding phases may be three times the normal and much higher values may be obtained by the injection of oestradiol

The concentration of inorganic phosphorus in the serum of adults is 2 5 to 3 5 mg per cent and it is all diffusible *in vitro* Since the solubility of $Ca_3(PO_4)_2$ is constant there is a dynamic equilibrium between calcium and phosphate ions that may be expressed by the formula $[Ca^{++}]^3 \times [PO_4 \ ] = K$ (constant) Therefore any rise in the concentration of phosphate ions will by the automatic play of physico chemical law cause a depression in the concentration of ionizable calcium and thus tend to cause tetany This is believed to be the sequence of events in hypo parathyroidism Experimentally the administration of sodium phosphate to animals will produce tetany by lowering the serum calcium indicating the primary factor of phosphate concentration increase

Metabolic and excretory studies in parathyroidectomized animals tend to prove the above theory Greenwald (1926 1931) showed that the immediate effects of parathyroidectomy are (1) a diminished urinary excretion of phosphorus and (2) a retention of phosphates in the blood Shelling and Asher (quoted by Shelling 1935) found in parathyroidectomized rats that the urinary excretion of phosphorus decreased considerably and phosphorus might disappear altogether from the urine The urinary calcium also decreased—an important finding contrary

to earlier investigations The faecal calcium and phosphorus content was not appreciably changed The feeding of calcium led to an increased excretion of phosphorus in the faeces as insoluble calcium phosphate The difference of results among various investigators is probably explained by the different amounts and proportions of calcium and phosphorus in the diets The alleviation of tetany apparently depended upon the excretion of phosphorus and the best therapeutic results were obtained with a diet low in phosphorus and relatively high in calcium in a ratio of 0 25 to 1 On such a ration the concentration of inorganic phosphorus in the serum decreased rapidly the serum calcium rose to normal levels and the excretion of phosphorus shifted from the urine to the faeces The cause of the failure of the parathyroidectomized rat to excrete phosphorus is not clear The kidneys show no pathological lesion and intravenous saline will produce a diuresis and increased excretion of phosphorus The latter is explained by the fact that the blood chlorides are low in parathyroidectomized animals

It is interesting that parathyroidectomized dogs will not partake of diets rich in phosphorus and low in calcium and if such a diet is introduced through a stomach tube spasm of the stomach and oesophagus results in vomiting This protective anorexia is a negative example of protective instincts and is comparable to the positive craving for salt that is sometimes met with in adrenal insufficiency

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PARATHYROID HORMONE (PARATHORMONE)

The final stage in elucidating knowledge of an endocrine gland is the preparation of an active extract This has been done in the case of the parathyroids although its chemical formula and synthesis have not yet been achieved As with other hormones numerous investigators have made claims which were not unjustified but could not produce consistent data to support them Finally Hanson (1925) and Collip (1925) produced potent parathyroid extracts which they were able to standardize A Hanson unit is one hundredth of the amount required to produce 1 mg rise in the serum calcium of a 15 kg dog 24 hours after parathyroidectomy A Collip unit is one hundredth of the amount which produces 5 mg rise in the blood serum calcium in 20 kg normal dogs over 15 hours A Collip unit is equal to 5 Hanson units

A single large injection given by subcutaneous or intra muscular route in normal animals leads to a gradual increase of serum calcium starting within a few hours reaching its maximum in 16 hours and falling to normal in the next 12 hours Diuresis begins within a few hours and is associated with an increased excretion of chlorides and phosphates An increased urinary excretion of calcium occurs some hours later after the serum calcium has risen The faecal excretion of calcium and phos phorus is not appreciably changed By the intravenous route parathormone produces a maximum rise of serum calcium in 4 hours but larger doses are required to attain the same degree of increase Tetany however may be relieved within 30 minutes of an intravenous injection and is associated with an immediate phosphate excretion and diuresis Parathormone is ineffective by mouth

Repeated parathormone injections cease to be effective after some 36 to 48 hours the serum calcium ceases to increase and then declines The initial fall of phosphorus concentration that follows parathormone injection gives place to a progressive increase Also the concentrations of urea and non protein nitrogen in the blood increase, and the sodium and chloride values decrease The blood becomes viscid Oliguria anuria anorexia vomiting diarrhoea muscular atony bradycardia and cardiac failure precede death Autopsy reveals metastatic

calcification in Bowman s capsule and the tubules of the kidneys and other soft tissues hyperaemia of the viscera haemorrhages into the stomach intestine and brain and decalcification of the bones with hyperaemia and haemorrhage in the marrow Renal damage and failure is probably the most important factor in causing death

In parathyroidectomized animals parathormone first pro duces a phosphate diuresis with a lowering of the high serum phosphate concentration and then a slow increase in the subnormal serum calcium concentration The phosphate diuresis starts within an hour, but the rise of serum calcium may be delayed for 24 hours and if the serum calcium rises above normal there may be increased excretion of calcium (Shelling 1935)

There are two theories as to the mechanism of action of parathormone The first or renal theory has already been discussed the primary action being an increased urinary excretion of phosphates Collip and Neufeld (1942) have further shown that parathyroid action cannot produce a rise in serum calcium if the excretion of urine (and therefore of urinary phosphate) is prevented by removing the kidneys of rats or dogs or ligaturing the ureters or renal blood vessels Neither is parathormone effective in normal animals if sodium and phos phate is given intravenously at a sufficient rate to prevent a fall of serum phosphate The second theory is that of direct action on bone (decalcification) Selye (1942) has again revived this older theory by showing that in nephrectomized rats parathormone will produce osteoclastic absorption of bone within 32 hours of injection providing that the parathyroids are intact Even so it is the kidneys that determine the bio chemical results of such mobilization of calcium and phosphates according to their selective excretion under parathormone influence

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THE PITUITARY PARATHYROTROPHIC HORMONE

There is a considerable amount of evidence in favour of the existence of a pituitary parathyrotrophic hormone and although it is not usually considered as conclusively proved the evidence appears sufficiently strong to me Clinically parathyroid hyper plasia or adenoma may be found in acromegaly (Cushing and Davidoff 1927) and in Cushing s syndrome (Cushing 1933) It is only in the latter condition that the radiological picture of the bones is comparable to that of primary hyper parathyroidism and at autopsy the bones may be decalcified and soft nevertheless although a negative calcium balance may be present the serum calcium is not raised and the serum phosphorus not lowered In acromegaly apart from the his tology of the parathyroids in some cases the evidence is still less tangible

There is only rarely evidence of the condition and function of the parathyroids in man when the pituitary gland has been destroyed or removed In a case of Simmonds s disease Gallavan and Steegman (1937) found two very small para thyroid glands composed almost entirely of irregular anasto matic groups of small transitional water clear cells In a man of 43 dying from a destructive craniopharyngioma under the care of Dr R A Rowlands and the writer (1942) Professor Turnbull recorded the presence of a few scattered pale oxyphil cells a relative preponderance of principal cells and the presence of alveoli lined with water clear cells In hypophysectomized dogs Houssay (1935) found involutionary changes in the para thyroid glands The cells decrease in size and the protoplasm shrinks and disappears leaving the nuclei in rows or heaps In parts of the gland the degeneration of the epithelial cells may be so complete that acellular structureless zones of irregular dimensions and of granular aspect are formed The ultimate lesion consists of a simple progressive atrophy of the cells with pyknosis and slow disintegration of nuclei

Anselmino Hoffman and Herold (1934) have shown that anterior pituitary extract can produce a considerable enlarge ment of the parathyroids in rats Hypertrophy and hyperplasia of the parathyroids have also been obtained in rabbits by the injection of pregnancy urine (Hertz and Kranes 1934) Further

the urine of patients with multiple parathyroid hyperplasia when extracted and injected into rabbits produces parathyroid hyperplasia (Hertz and Albright 1934) Houssay (1935) records an increase of blood calcium lasting several hours in dogs following the injection of an anterior pituitary extract and not being obtainable after parathyroidectomy The experimental *evidence therefore is strongly in* favour of the existence of a pituitary parathyrotrophic hormone

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VITAMIN D AND THE PARATHYROIDS

Although both vitamin D and parathormone raise the concentration of serum calcium and present similar clinical pictures of overdosage their mode of action is different That of parathormone has been dealt with that of vitamin D is to promote the absorption of calcium and phosphate from the bowel Deficiency of parathormone is manifested by a low serum calcium and a raised serum phosphorus In vitamin D deficiency both the serum calcium and the serum phosphorus concentrations are lowered or the latter may be normal There is however some relation between the parathyroids and vitamin D deficiency since the latter may result in parathyroid hyperplasia and hyperfunction Parathormone however is unsuitable therapy for vitamin D deficiency since it tends to mobilize calcium from bones already seriously deficient in calcium content *Therapeutic amounts of vitamin D cause a positive balance* of calcium and phosphorus with resulting calcification of bone whereas parathormone produces a negative balance and retards ossification Similarly the increase of serum calcium produced by vitamin D is accompanied by an increase in serum phosphorus

whereas that produced by parathormone is preceded by a decrease of serum phosphorus due to phosphate excretion in the urine

These two actions are reflected in the changes in composition of the bones of rachitic rats vitamin D producing a considerable increase in the calcium phosphorus and ash content of such bones whereas parathormone produces a decrease in these values

Although the parathyroids may undergo hyperplasia in vitamin D deficiency disorders e g rickets osteomalacia (Erdheim 1906) they somewhat paradoxically undergo similar change when vitamin D is given in excess (Grant and Gates 1924) In fact they protect the organism against an excess of vitamin D by getting rid of the excessively retained phosphorus by urinary excretion Shelling (1932) found that an amount of vitamin D which on a certain diet would produce metastatic calcification in parathyroidectomized rats failed to do so when the parathyroids were intact and therefore able to undergo a protective hyperplasia

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B CLINICAL

CHAPTER XXXI

HYPERPARATHYROIDISM

(Generalized Osteitis Fibrosa Cystica von Recklinghausen's Osteitis Fibrosa)

(a) Definition

GENERALIZED osteitis fibrosa cystica is a metabolic disorder due to excessive secretion of parathormone resulting in a raised serum calcium negative calcium balance and progressive generalized decalcification of bone frequently associated with giant celled osteoclastic tumours and cysts

(b) Historical

In 1891 von Recklinghausen included a probable case of this disease among an undifferentiated motley of bone disorders but the first recorded case is said to have been described by Courtial in 1700 Erdheim in 1906 first drew attention to enlargement of the parathyroids in cases of alleged osteomalacia some of which were probably osteitis fibrosa cystica He thought the parathyroid enlargement was secondary and although this is so in osteomalacia it is primary in generalized osteitis fibrosa cystica Schlagenhaufer urged this view in 1915 and in 1926 Mandl explored the neck of a patient with osteitis fibrosa cystica and removed a parathyroid tumour after which improvement resulted By 1934 Ravine and Lyon were able to trace 82 parathyroidectomies in the literature

(c) Pathology

In 32 cases of hyperparathyroidism Hunter and Turnbull (1931) found that 24 were due to a single parathyroid tumour 3 had two parathyroid tumours and the remainder were due to hyperplastic parathyroid glands or were undetermined When hyperparathyroidism is secondary to chronic nephritis or vitamin D deficiency the parathyroid glands show hyperplasia

In primary hyperparathyroidism due to a parathyroid adenoma the remaining parathyroid glands may show involution

comparable to that found in the opposite adrenal gland when an adrenal cortex tumour is present The largest tumour recorded weighed 26 gm and measured 7×5×2 cm The severity of the disease is not related to the size of the para thyroid adenoma and a small tumour weighing 1 gm has produced a most crippling disease Histologically a parathyroid adenoma (or hyperplasia) may contain chief or principal baso phil cells pale oxyphil and dark oxyphil cells or one or more of such cells may predominate It is probable that the cells represent different phases of activity and are not essentially and constantly different cells (see Physiology section for histology)

Bone changes Snapper (1940) summarizes the bone changes somewhat briefly as follows

(1) proliferation of osteoclasts which erode bone with result ing decalcification and proliferation of fibrous tissue in the Haversian canals
(2) cyst formation
(3) formation of giant cell tumours—osteoclastomas

Osteoclastomas may be minute or very large They are areas occupied by numerous large osteoclasts among fibrocytes that are less differentiated than in the remainder of the fibrous marrow Their disappearance after excision of a parathyroid adenoma suggest that they are areas of osteogenetic marrow that have been stimulated by excessive parathyroid secretion to an exaggerated osteoclastic activity In fact all the abnormalities in the bone could be attributed primarily to parathyroid secretion causing an excessive stimulation of osteoclastic resorption (Turnbull 1930) The giant cells of the bone marrow dissolve bone because this is their normal function Osteoclastomas are not malignant

Both osteoblasts and osteoclasts are cells of the fibrous reticulum of the marrow in a stage of functional activity both physiologically and pathologically the former are concerned with bone deposition and the latter with bone resorption Normally these two processes are well balanced Turnbull (1930) points out that there is a close resemblance between the histo logical processes of generalized osteitis fibrosa and in the osteitis deformans of Paget but in fibrosa resorption greatly exceeds

apposition (or deposition) while in Paget's the opposite is true or the processes are equally balanced

In hyperparathyroidism fibrosis of marrow is a conspicuous feature and usually very widespread Cysts are usually very numerous Larger cysts have a wall of dense often hyaline collagenous fibrous tissue In smaller ones the wall does not differ from the surrounding fibrous tissue Cysts most frequently occur in the larger areas of fibrous marrow that are free from bone but they may be in bone itself or in osteoclastomas They (the cysts) contain a thin albuminous coagulum or fibrinous clot

In osteitis fibrosa diffusa the bone matrix that is being laid down is normally calcified and the osteoid seams are of normal width whereas in osteomalacia there are wide osteoid seams and calcification is deficient or absent All bone when first formed is osteoid and becomes calcified later

Kidneys Calcium deposition may occur in any of the viscera and in the blood vessels but the kidneys appear to be the commonest site and it is here that most damage may be done They may show diffuse microscopic deposition of calcium or multiple minute calculi or sometimes large calculi With diffuse calcium deposition there results interstitial tissue fibrosis round celled infiltration hyalinized glomeruli and thickened arterioles If the process has been going on for some years the ultimate picture clinical and pathological may be that of chronic interstitial fibrosis On the other hand the renal condition may be primary and the parathyroid glands undergo secondary hyperplasia in an attempt to excrete the retained phosphates

(d) Incidence

The disease is usually found in the third or fourth decade but may be present at any age and Fig 56 illustrates its onset in childhood It is said to be more common in women than in men but owing to its rarity such preponderance is not necessarily encountered in any group of cases

(e) Clinical Picture

The onset is usually gradual and insidious although the first major manifestation may be sudden and dramatic e g

a pathological spontaneous fracture or renal colic A not uncommon presentation is a bone tumour, which on section is



FIG 56 HYPERPARATHYROIDISM—generalized osteitis fibrosa Parathyroid tumour Boy aged 13 Note the deformities of the bones and dwarfism Serum calcium 16 6 mg plasma phosphorus 3 mg per 100 c c X rays showed generalized decalcification of bones with cyst like areas and calcium deposition in the kidneys The tumour ($2 \times 1\ 8 \times 0\ 8$ cm) was removed by Sir James Walton (By courtesy of Dr Donald Hunter)

seen to be an osteoclastoma or the long bones the chest and spine may become thickened bent or deformed Increasing asthenia and wasting with muscular and bony pains may be the predominating features, and give no obvious indication of the

underlying disorder A more complete clinical picture can be synthesized from consideration of the various systems affected



FIG 57 HYPERPARATHYROIDISM Osteoclastoma of jaw in a woman of 48 being the first manifestation of hyperparathyroidism due to a parathyroid tumour (By courtesy of Professor H Cohen *Brit J Surg* 1933 xx 47)

Skeletal The skeletal changes are characteristically well marked and generalized but not necessarily uniform In some patients however the bony changes as seen by X ray may be minimal The more usual finding of extensive decalcification results in rarefaction and softening of the bones which become bent and deformed The lower limbs tend to become bowed and

walking becomes increasingly difficult the gait being awkward and waddling In the later stages the patient is bed ridden Osteoclastomas form swellings at the ends and in the shaft of long bones on the jaw and anywhere on the skull The vertebrae tend to be absorbed and collapse with resulting kyphosis and considerable loss of height Pathological fractures occur and delayed union is frequent The jaw may become massive and its deformity leads to displacement and falling out of teeth but the latter are not decalcified The bones and osteoclastomatous swellings are often tender especially on pressure Pain in the lower back may be severe Clubbing of fingers may occur from resorption of the terminal phalanges It is important to remember however that the bone changes may be inconspicuous

Radiography All the bones show great rarefaction Osteo clastomatous swelling and cyst formation are seen in various parts of the skeleton The skull shows a granular appearance and lack of differentiation between the tables Recent and old fractures of the long bones are revealed The terminal phalanges may be resorbed

Muscles Hypotonicity of the muscles is present in contrast to the hypertonicity and irritability of the muscles in the opposite condition of tetany The patient feels weak and is incapable of muscular effort Considerable wasting of the muscles is not infrequent Spontaneous pains occur simulating rheumatism pseudo arthritis and neuritis and the muscles may be tender to touch The joints may be excessively mobile

Gastro intestinal Anorexia and intermittent nausea with progressive loss of weight are frequent features Vomiting may be intractable and is ascribed by Snapper (1940) to the hyper calcaemia Abdominal pains and cramps are met with and gastric ulcer or appendicitis may be simulated Constipation is usual Dry mouth and polydipsia are the result of polyuria which latter is an attempt to excrete the excess of serum calcium in soluble form

Heart and lungs Dyspnoea and cyanosis may result from calcium deposition in the heart and lungs as well as from bony chest deformities and muscular weakness Tachycardia is not uncommon

Blood The viscosity of the blood is increased Destruction

of the bone marrow may result in a secondary anaemia and in leucopenia

Nervous system Though patients may be nervous and irritable being sometimes confused mentally organic lesions of the central nervous system are not present Apathy is not infrequent Symptoms of tetany are met with after removal of a parathyroid tumour or may rarely be present terminally in hyperparathyroidism complicated by renal insufficiency

Metabolism Characteristic biochemical findings are a raised serum calcium a lowered plasma phosphorus a raised plasma phosphatase and a negative calcium balance The serum calcium may be only slightly raised e g 12 mg per 100 c c (normal 9 to 11 mg) or it may be as high as 26 mg per 100 c c It is advisable to repeat the estimation of serum calcium at least on two occasions in a doubtful case The plasma (or serum) phosphorus is usually below 2 5 mg per 100 c c and may be as low as 1 mg If however kidney function has been impaired by the deposition of calcium (see below) the plasma phosphorus may be normal or raised (Plasma phosphorus is more accurately assayed than serum phosphorus as the plasma is more rapidly separated from the corpuscles which take up phosphorus)

The plasma phosphatase is nearly always appreciably raised in hyperparathyroidism but this is a measure of bone activity (destruction or deposition) regardless of the cause of such changes Thus high values are also found in osteitis deformans and in rickets &c Phosphatase is an enzyme capable of splitting organic phosphorus compounds and liberating inorganic phosphorus Robison (1923) first drew attention to this enzyme in nearly all tissues e g liver kidneys intestinal mucosa Kay applied his method of assay to plasma and expressed enzyme activity in terms of the number of milligrams of phosphorus liberated as inorganic phosphate from excess of sodium β glycerophosphate in 48 hours at 38 C and at pH 7 6 by 1 c c of plasma the normal being 0 2 mg Bodansky (1933) simplified Kay s method and expressed his unit in terms of mg of inorganic phosphorus liberated in one hour per 100 c c of serum He gives normal values for adults as 1 5 to 4 units and for children as 5 to 12 units In hyperparathyroidism values range around 20 Bodansky units but depend upon the degree of bone change Another unit is the King Armstrong with a normal range of

4 to 8 The plasma phosphatase is unlikely to be much above normal where the bone changes are minimal

In normal people 80 per cent of the calcium is excreted in the faeces and 20 per cent in the urine whereas in hyperparathyroidism 80 per cent of the calcium is excreted in the urine and only 20 per cent in the faeces and further in hyperparathyroidism there is a marked negative calcium balance the urinary calcium being three to five times that of a normal control e g 1 8 gramme compared with 0 5 gramme over a 3 day period on a 100 mg daily calcium intake Fortunately the faecal calcium in hyperparathyroidism is not very different from normal except when renal disease complicates the picture and calcium excretion is deflected from the urine to the faeces In most cases however it is sufficient to estimate urinary calcium Faecal calcium represents non absorbed as well as excreted calcium Its estimation is technically laborious Calcium balance experiments are usually undertaken over a 3 day period and if faecal estimation is included the oral administration of 0 3 gm of carmine alum every 3 days permits the division of such periods by its colour appearance in the faeces It is necessary to place the patient on a standard calcium diet usually a low one of 100 mg calcium per day the normal intake being 700 to 1 000 mg Simmonds (1931) gives a 100 mg calcium diet as

Breakfast 30 gm bread 100 gm banana 15 gm butter
Dinner 75 gm lean meat 100 gm potato 30 gm rice 100 gm apple
Tea 30 gm bread 15 gm honey 15 gm butter
Supper 9 gm chicken 50 gm potato 100 gm apple 50 gm banana
Tea sugar and lemon juice as desired

Kidneys and renal function Polyuria and polydipsia and nocturia are frequent symptoms and do not indicate renal disease but are manifestations of an attempt to excrete the increased serum calcium in soluble form The kidneys however are frequently involved in hyperparathyroidism and the first manifestation is often renal e g haematuria, renal colic renal calculi, or chronic nephritis The excess of calcium in the blood may be deposited in all the soft tissues of the body or selectively in the kidneys or in the arterioles When the kidneys are involved the calcium deposition may be in diffusely scattered minute particles (calcinosis) or multiple calculi often very large

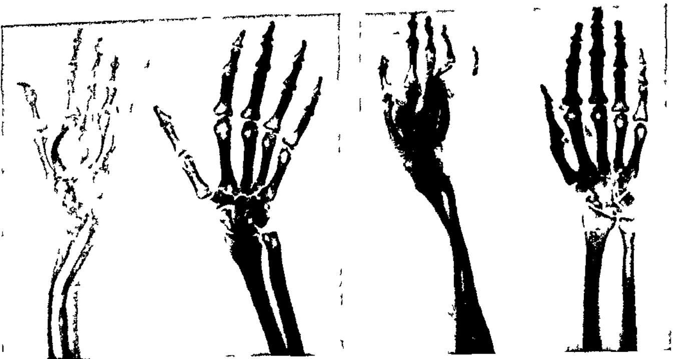

(a) (b)

FIG 58 HYPERPARATHYROIDISM (a) Showing decalcification of the bones of the forearm and hand and cyst formation with control (b) The same 12 months after operation (By courtesy of Dr Donald Hunter *Proc Roy Soc Med* (1935) xxviii 55)

may accrue either in the kidney substance, or the pelvis or both These changes are sometimes found in the absence of gross skeletal changes Albright and Bloomberg (1934) consider that hyperparathyroidism is such a frequent cause of renal calculus that its presence must be ruled out in every such case This is also done in the investigation of every case of renal calculus in the Urogenital department of the Mayo Clinic

Where diffuse calcinosis is present the kidneys undergo fibrosis and hyalinization and the ultimate clinical and pathological picture is that of chronic interstitial nephritis The deposition of calcium in the arterioles may lead to their degeneration and hyaline occlusion Hypertension develops and may be severe The patient dies in uraemia or from intercurrent infection Although no impairment of renal function may be observed at the time of removal of a parathyroid tumour and although such an operation is usually followed by a complete control of the primary hyperparathyroidism yet chronic nephritis may develop some years later and one must assume that initial irreversible changes were sufficiently severe to progress to fibrosis without further calcium deposition After removal of a parathyroid tumour renal calculi usually disintegrate rapidly but this is not always the case (Johnson 1939)

A further complication of this relationship between the parathyroids and the kidneys is the fact that in chronic renal disease of any aetiology parathyroid hypertrophy and hyperplasia may be a secondary effect in an endeavour to excrete the retained phosphorus (Pappenheimer and Wilen 1935) Such hyperplasia may also be found at autopsy when a parathyroid adenoma has been removed for hyperparathyroidism and chronic renal changes have developed later Albright (1936) has described a case in which chronic hyperparathyroidism with hyperplasia of the parathyroid glands developed 20 years after an idiopathic acute nephritis which became chronic He calls the condition renal osteitis fibrosa cystica and defines the salient features of the syndrome as marked renal insufficiency which has lasted a long time phosphate retention with a high serum inorganic phosphorus level a slight reduction in the serum calcium level a marked acidosis calcium deposits in the neighbourhood of joints extreme calcification of the media of all arteries (Mönckeberg type of arteriosclerosis) osteitis fibrosa

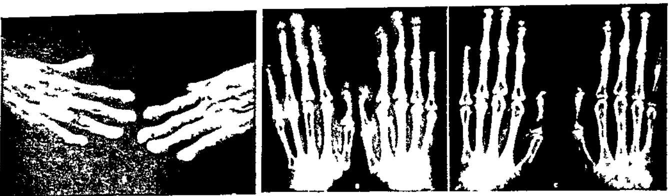


FIG 9 HYPERPARATHYROIDISM Clubbing of the fingers in hyperparathyroidism due to decalcification of the terminal phalanges as shown in X ray (left) while recalcification is shown in the further X ray (right) taken nine months after removal of a parathyroid tumour (By courtesy of Dr A B Gutman *J Amer Med Ass* (1934), ciii 87)

generalisata of all bones and enormous enlargement of all parathyroid tissue He further supposes that renal rickets is really a variety of this syndrome in childhood the bone changes being secondary to a chronic nephritis and produced by secondary parathyroid hyperplasia

When investigating a supposed case of hyperparathyroidism renal function should always be examined since occult renal insufficiency will tend to alter the characteristic blood chemistry Thus the plasma phosphorus instead of being subnormal e g 1 5 mg per 100 c c may be considerably raised e g as much as 8 mg and a secondary effect of this is to depress the serum calcium which instead of being say 16 mg per 100 c c may be normal or even subnormal e g 8 5 mg per 100 c c since the physico chemical equation $Ca \times P = K$ The biochemical findings might therefore be held to exclude a parathyroid adenoma and this false conclusion be further supported by the absence of a negative calcium balance as judged by urinary estimation the calcium excretion being deflected to the faeces

Some classical examples of hyperparathyroidism complicated by renal disease or vice versa are given in an appendix to this section to illustrate the points made in the general discussion

(f) Diagnosis

The disease may present itself in many forms e g rheumatism spontaneous fracture a bony swelling (osteoclastoma) on long bones jaw or skull weakness and fatiguability gastro intestinal disorder renal colic haematuria or nephritis It is a condition therefore which should also be in the minds of physicians and surgeons who are not especially interested in endocrinology Most cases will show generalized osteoporosis on radiographic examination but such bone changes may be minimal The skull frequently gives a characteristic granular radiographic picture Calcium deposits may be seen in the kidneys and other viscera Investigation of the blood chemistry indicates a raised serum calcium and a low serum phosphorus and calcium balance experiments show a negative balance with excessive urinary excretion of calcium The plasma phosphatase is almost invariably raised The effect of renal disease on the characteristic blood mineral metabolism is discussed in a previous section and an atypical chemical picture does not

contra indicate the diagnosis of hyperparathyroidism if renal insufficiency is a complication Liu (1940) has also pointed out that where hyperparathyroidism is associated with hypovitaminosis D the serum calcium may be normal and no calcium excreted in the urine However the giving of calciferol in adequate dosage to correct the hypovitaminosis will be followed by a return to the characteristic chemical picture of hyperparathyroidism

Unlike a thyroid adenoma a parathyroid adenoma is usually not palpable and must be sought for at operation Rarely however such a parathyroid adenoma may be palpable clinically before operation

A number of conditions which bear a possible resemblance in one or more clinical or radiographical or biochemical features to osteitis fibrosa diffusa are considered below

(1) *Albright s syndrome* This was described by Albright and colleagues in 1937 under the title Syndrome characterized by osteitis fibrosa disseminata areas of pigmentation and endocrine dysfunction with precocious puberty in females (Fig 60) Falconer and others (1942) showed that such precocious puberty also occurred in boys The main characteristics are (*a*) multiple bone cysts which have a distribution suggesting a relation to nerve roots or to an embryological defect in the myotomes (*b*) areas of pigmentation which have a distribution suggesting some connexion with the bone cysts the pigment is melanin (*c*) precocious puberty with premature union of the epiphyses and ultimate dwarfism In Albright s four cases the first menstruation was observed at 1 3½ 3½ and 7 years of age respectively Normal pregnancy may occur in adult patients The blood calcium and phosphorus and the calcium balance are normal but the phosphatase may be raised Falconer described other features e g massive bony deformity of head with resulting optic atrophy and of the jaw resembling leontiasis ossea acromegalic features enlargement of thyroid unilateral exophthalmos and wide separation of the eyes

Steinberg and Joseph (1942) describe an autopsy in a girl of 12 suffering from Albright s syndrome complicated by hyperthyroidism Pigment appeared at the age of 2 and that year she began to menstruate Within the next few years she had multiple pathological fractures At the age of 9 thyrotoxicosis made its



Fig 60 Albright's Syndrome Girl aged 3½ years showing segmental osteitis fibrosa segmental pigmentation and sexual precocity which latter is always present in girls but only occasionally in boys calcium metabolism normal (By courtesy of Dr Fuller Albright New Eng J Med (1937) ccxvi 17)

appearance B M R plus 65 per cent There was no exophthalmos Calcium and phosphorus studies and balance experiments were normal as was the phosphatase 0 2 Kay units in spite of widespread bone disease At 11 she was operated on for a twisted cystic right ovary She died the following year of broncho pneumonia Autopsy showed mature cystic ovaries with however no corpora lutea a hyperplastic thyroid an enlarged thymus and hypertrophic lymphoid structures a narrow adrenal cortex the glomerulosa zone being ill defined and somewhat atrophic the fascicular zone narrow but the pigmented reticular zone prominent remarkable hyperplasia of the basophil cells (50 per cent) of the pituitary with a tendency to adenomatous formation and vacuolization but completely normal parathyroid tissue Of the bone the authors state The disease of the bones is patchy and is characterized by lacunar osteoclastic resorption fibrosis of marrow spaces osteoblastic repair and cyst formation The pathological bone picture resembles in some respects von Recklinghausen s disease although the tempo of bone resorption is somewhat slower

(2) *Focal osteitis fibrosa* This condition may be found in one or more bones and its incidence is chiefly in adolescence although it may appear at any age The commonest clinical manifestation is spontaneous fracture General symptoms and constitutional disturbance are absent The cause is unknown and there is certainly no obvious connexion with the parathyroids since the calcium and phosphorus serum concentration and the calcium balance are normal Where several bones are affected the plasma phosphatase may be raised

(3) *Paget s osteitis deformans* Paget who described the disease in 1877 believed the condition to be inflammatory in origin and although this is not generally held to be the case to-day no aetiological cause metabolic or otherwise has been substantiated The writer with his colleagues Kay and Riddoch observed and investigated 34 cases of this disease in 1926 Its onset is usually in middle life although it may be first observed in the third or eighth decade of life The average age of onset in our series was 46 the youngest 30 and the oldest 60 years of age There were 18 females and 16 males A brother and sister and their mother constituted the only example in

this series of a familial incidence but others have observed such familial tendencies in the minority of cases

The onset of osteitis deformans is usually insidious and the progress gradual The disease may be limited to one tibia for some years but is more usually generalized The vault of the skull is considerably thickened enlarged and deformed and the face seems small in comparison to the top heavy head Owing to phases of softness of bones the spine and shoulders bend and in advanced cases the patient s stance is Simian in character The legs become bowed and may cross over in scissor fashion so that the patient may become bedridden contrary to Paget s original observation that the limbs how ever mis shapen remain strong and fit to support the trunk Generalized pains of the bones are common and may be very severe especially in the legs Fractures following slight trauma occurred in five of our patients Sarcomatous change in a long bone rarely supervenes Serum calcium and phosphorus con centrations are normal but a negative calcium balance is not infrequent and the plasma phosphatase is always raised No pathological changes in the parathyroids have been recorded Radiologically areas of rarefaction and increased density are seen side by side and a characteristic fluffy cotton wool appearance may be seen in the pelvis and skull Complications are arterial degeneration and rarely spastic paraplegia or optic atrophy due to bony compression of nerve tissue

(4) *Carcinomatosis of bones* If metastases from an undetected primary carcinoma e g prostrate are numerous a radiological resemblance to osteitis fibrosa diffusa may be observed How ever the chemical picture is not characteristic of hyperpara thyroidism the serum calcium and phosphorus being normal The phosphatase is raised as in most generalized bone disturbances

(5) *Multiple myelomatosis* The presence of multiple marrow tumours may simulate osteitis fibrosa diffusa Progressive anaemia and cachexia associated with a high incidence of fractures are major features If there is much bone destruction the serum calcium may be high and a negative calcium balance exists The plasma phosphorus is never low It is normal or above normal when the kidneys are involved Bence Jones protein in the urine is characteristic

(6) *Osteomalacia* This vitamin D deficiency disorder is a

rarity in England but may be found as a result of gastro intestinal disorder not permitting adequate absorption e g chronic steatorrhoea The serum calcium and phosphorus are both low or one may be normal but never are they above normal The urinary calcium is low and the faecal calcium high The plasma phosphatase is raised

(7) *Generalized osteoporosis resulting from a low renal threshold* Hunter (1935) recorded two such cases due to the kidneys permitting an excess of calcium to escape into the urine The serum calcium however is not raised The renal aetiology is put forward as a suggestion Robertson (1941) records that It has been stated that a serum calcium of 8 5 mg per 100 c c is the threshold value for urinary calcium excretion and that below this level the calcinuria is negligible This was not suggested by his observations in a patient with a serum calcium of 5 5 mg per 100 c c in whom 23 per cent of the calcium was excreted in the urine which is a normal proportion

(8) *Thyrotoxic osteoporosis* The clinical picture is that of thyrotoxicosis but some 40 per cent of patients show some rarefaction of bones and a negative calcium balance but normal serum calcium and phosphorus values Thyroidectomy or thiouracil corrects the osteoporosis and negative calcium balance which are not related to the parathyroids but to the increased metabolism of hyperthyroidism

(9) *Senile osteoporosis* Generalized osteoporosis may be found in senile people or in younger people confined to immo bility for long periods The cause is undetermined but the diminution of gonadal secretion especially oestrogens has been postulated

(10) *Fragilitas Ossium* Multiple fractures occur *in utero* in infancy and childhood There is no disturbance of calcium or phosphorus metabolism and no known endocrine cause The sclerotics of the eye are blue

(g) Course and Prognosis

In the absence of correct treatment hyperparathyroidism is inevitably progressive Weakness and deformity of the bones eventually render the patient bedridden and intercurrent infec tion such as pneumonia leads to death Sometimes the kidney lesion is the most severe aspect and terminal uraemia results

(h) Treatment

The condition cannot be controlled medically Radiation of the parathyroids is sometimes helpful but rarely sufficiently



FIG 61 FRAGILITAS OSSIUM Girl aged 13 syndrome consisting of fragility of bones and multiple fractures from birth or even intra uterine life with blue sclerotics normal calcium balance and no obvious endocrine defect This is not an endocrine disorder as far as is known

effective If the clinical and biochemical pictures indicate hyperparathyroidism the neck should be explored and the adenoma removed Should the parathyroids appear normal the search should extend downwards to the retrosternal region for an aberrant adenoma If the surgeon is convinced that no

adenoma is present, two parathyroids should be removed as some degree of benefit may result

If an adenoma has been removed the post operative period needs careful attention since tetany is a frequent complication Intramuscular and in emergency intravenous calcium gluconate 20 c c of 20 per cent solution should be given daily or several times a day and large doses of calcium by mouth e g ½ ounce of calcium gluconate four times daily Parathormone 20 units subcutaneously daily is a temporary therapeutic help given in the presence of tetany for the first week or so but it is obviously illogical to mobilize calcium from bones already decalcified Large doses of vitamin D accelerate the utilization of calcium and ultra violet light is a valuable addition The tendency to tetany becomes less and often disappears as the remaining parathyroid bodies undergo secondary hyperplasia The manifestations of subnormal calcium concentration may be psychotic rather than tetanic and are similarly abolished when the serum calcium reaches normal values again The more immediate results of operation are a disappearance of pain in the limbs an increase in strength the loss of gastro intestinal symptoms and the cessation of polyuria and polydipsia Recalcification of bones may take several months or more and although further deformity or fractures are unlikely the existing malformations may prevent proper ambulation Osteoclastomas tend to disappear in a few weeks Renal calculi may disintegrate and be passed as gravel Chronic nephritis if of recent onset may improve Cataract or lenticular opacities may occur if calcium is not given in adequate doses after operation Menstruation if previously scanty or absent returns to normal The serum calcium falls immediately and subnormal levels are the cause of the tetany the serum phosphorus tends to return to normal and the increased calcium excretion ceases The serum phosphatase usually remains raised only gradually falling after a period of months or more it is therefore more a measure of degree and extent of bony change rather than of the excess of parathyroid hormone

(i) Appendix Hyperparathyroidism and Renal Disease

Albright s case (1936) Renal osteitis fibrosa cystica Man of 45 years admitted to hospital for generalized itching and painful swelling (calcium deposits) on flexor aspects of fingers of right hand At age of 22

he had acute nephritis with oedema followed by subacute and chronic nephritis His urine now showed albumen and casts and specific gravity was 1 010 Blood urea 120 mg per cent renal function tests 10 per cent of normal I 9 8 and Ca 8 2 mg per cent phosphatase 9 4 Bodansky units carbon dioxide combining power of plasma decreased 37 8 vol per cent Hypertension 165/90 Death in coma Autopsy Chronic glomerular nephritis all four parathyroids tremendously enlarged one weighing 5 gm (normal 60 mg) all vessels showed medial calcification bone changes characteristic of hyperparathyroidism

Comment Primary chronic nephritis with secondary hyperparathyroidism comparable to the experimental hyperparathyroidism produced in animals by injecting phosphates or creating a condition of chronic acidosis

Downs and Scott (1941) Hyperparathyroidism with adenoma causing renal failure and secondary hyperparathyroidism Man of 50 years with pain in right loin 2 years history of renal colic weakness and fatiguability and loss of weight History of an attack of renal colic with the passage of stones 20 years previously and of hypertension for 15 years He now had hypertension of 190/130 and the urine showed albumen and granular casts X ray showed mottled areas of calcium deposition in both kidneys and general decalcification of bones Blood urea 78 calcium 7 5 phosphorus 4 1 mg per cent A few months later he died in uraemic coma the terminal serum calcium being 5 8 phosphorus 7 6 and tetanic spasms with positive Chvostek and Trousseau signs making their appearance

Autopsy One parathyroid adenoma and three hyperplastic parathyroid glands atrophic kidneys with hyalinized glomeruli and tubules and scattered calcified areas No gross bone changes

Comment The long history of renal calculi and the renal calcinosis together with a parathyroid adenoma suggest that the latter was the primary condition and that the parathyroid hyperplasia was secondary to the renal insufficiency which developed from the renal calcinosis The effect of renal insufficiency in distorting the blood chemistry of hyperparathyroidism is seen

Johnson (1939) Primary hyperparathyroidism with extensive renal calcification and secondary hyperplasia of the parathyroids Man of 34 from the age of 30 complained of weakness loss of weight and polyuria and sustained a pathological fracture The skeleton at that time showed generalized osteoporosis the urine showed a faint trace of albumin and some casts B P 150/90 X ray of renal tract revealed a horse shoe kidney with many areas of calcification Serum Ca 15 7 P 2 6 phosphatase 34 Bodansky units negative Ca balance A parathyroid adenoma was removed followed by transient tetany and a return to normal chemistry Four years later patient returned complaining of headaches B P 210/120 blood urea 79 albuminuria no casts Ca 10 5 P 6 phosphatase 5 4 X ray of kidney showed the condition to be the same He died in uraemia

Autopsy Kidneys showed diffuse calcinosis with hyalinized glomeruli and tubules and inspissated casts Thickening calcium deposition and

degeneration of arterioles No gross changes in bones Hypertrophy and hyperplasia of remaining parathyroid tissue

Comment Primary parathyroid adenoma with renal calcinosis continuing after removal of the adenoma Chronic renal insufficiency followed by secondary parathyroid hyperplasia

Author's case Woman 45 At age of 41 (1942) admitted under surgical colleague Mr F W M Pratt with lump on left tibia found on biopsy and subsequent removal to be osteoclastoma Radiography then revealed generalized osteitis fibrosa cystica calcium depositions and one single calculus in kidneys Serum Ca 15 8 P 2 5 phosphatase 61 Bodansky units Removal of an enlarged hyperplastic parathyroid 4 4 gm by Mr Pratt was followed by transient tetany and subsequent return of blood chemistry to normal The urine was normal B P 140/80 Six months after operation the bone radiographs showed approximation to normal In November 1945 she complained to her family doctor Dr R F Davie of frequency and dysuria Her blood pressure was then 115/70 and several previous readings had been normal In June 1946 she fell and severely bruised her arm and was admitted under my care at Willesden General Hospital She then showed hypertension 240/160 bilateral pallid disks and fundal exudates albuminuria and granular casts Radiographs showed no evidence of renal calculi although some mottling of kidney substance was present Blood urea 86 mg per cent serum calcium 12 4 phosphorus 8 mg per cent urea clearance 17 8 per cent of normal plasma phosphatase 6 King Armstrong units (normal 4 to 10 units) The calcium phosphorus and phosphatase values were repeated on several occasions and gave very similar values There was a negative calcium balance 854 mg of calcium being excreted in the urine in 72 hours with an intake of 100 mg calcium per day Radiographs showed a return of generalized decalcification of bones but of milder degree than before operation

Comment This is undoubtedly a case of primary parathyroid tumour It would appear that the renal calcinosis had initiated changes in the kidneys which in spite of removal of the tumour progressed to chronic nephritis after a clinical latent period of some years Secondary hyperplasia of parathyroids then followed It is of interest that in spite of the high P values the calcium was still above normal concentrations

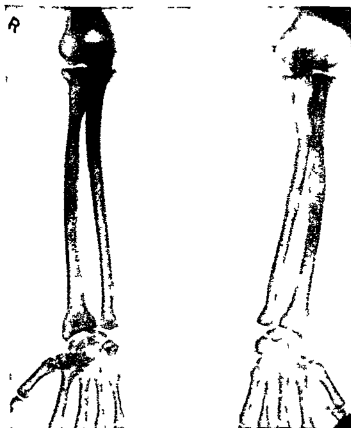
Addendum Death in uraemia autopsy showed multiple minute calcium deposits in fibrotic kidneys considerable secondary hyperplasia of the remaining three parathyroid glands On lifting the brain a large lobulated pituitary tumour presented lying mostly above the sella turcica which was widened and its walls thinned The optic chiasma was stretched across the posterior portion of the tumour The whole tumour measured 2 [illegible] 5 cm and a portion of it 1 1 × 1 5 cm lay wholly in the pituitary fossa The cut surface of the tumour was pale and homogeneous occasionally mottled with haemorrhage Histologically it was seen to consist of a chromophobe adenoma with a very small rim of the original anterior lobe of the pituitary at the base

(This case will be published separately with full details)



(a) (b)

Fig 6 Hyperparathyroidism in a woman of 41 (author's case) (a) X ray skull (1942) when diagnosed showing typical mottling and granular appearance (b) Three years later showing increased density and delineation of skull bone but residual mottling in the upper area Pituitary fossa is seen to be slightly enlarged and a pituitary tumour was *found at* autopsy (see full description of case p 331)



Fi 6 c

Same case sl owing d al if at on f the ra tius and ulna and y t formation (left) an l n ea l den ty three y ars later (right)



FIG 63 KIDNEYS (from author's case of Hyperparathyroidism p 331) Radiograph after removal from the body (autopsy) showing scattered multiple deposits of calcium in both kidneys patient died in uraemia

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states that the gland cells of parathyroids are replaced by fibrous tissue or fatty tissue or a round celled infiltration, or may be congenitally absent Sutphin Albright and McCune (1943) record a post mortem on a boy who died with idiopathic hypothyroidism the parathyroids showing complete aplasia of the epithelial cells and their replacement by fatty cells The same authors quote another case in which there was no evidence whatsoever of parathyroid tissue at autopsy suggesting a congenital absence They also observed idiopathic hypoparathyroidism in a boy and his two sisters the three being the children of two first cousins The disorder happened to be associated with moniliasis (a fungus infection) of the tongue and nails but no real connexion between the two conditions is claimed Lachman notes that idiopathic hypoparathyroidism may arise in infancy or at any time during life and may be familial The symptoms may be acute or chronic and are not essentially different from any other type of tetany Himsworth and Maizels (1940) reported a most interesting case of congenital thyroid (partial cretinism) and parathyroid deficiency in a boy who suffered from hypocalcaemic tetany and grand mal and developed cataracts at the age of 12

(c) *Rickets osteomalacia (adult rickets) steatorrhoea* In these conditions there is deficient absorption and utilization of calcium Infantile spasmophilia may also be included

(d) *Pregnancy lactation and menstruation* The increased demands for calcium in these conditions probably render a latent tetany manifest Deficient calcium in the diet and deficient sunlight and vitamin D may be the predisposing causes

(e) *Alkalosis* which acts by reducing the ratio of ionized to non ionized calcium

(i) Excessive vomiting or gastric lavage e g pyloric or intestinal obstruction
(ii) Hyperpnoea (1) hysteria
(2) voluntary
(3) post encephalitis lethargica
(iii) Excessive alkaline treatment of gastro duodenal ulcer
(iv) Alkalies in nephritis

(f) *Infections* This effect is rarely seen with modern improved diets and is probably a manifestation of latent tetany

The function of the parathyroids is diminished by infections as is the pancreas in diabetes mellitus

(g) *Epidemic and occupational* This occurs in parts of Europe being probably associated with deficient diet and sunlight

(h) *Excessive phosphorus in diet* This is largely theoretical except in cattle The high phosphorus depresses the calcium level The occurrence of phosphorus tetany is however of considerable interest as we have seen in the physiology section that the primary action of the parathyroids is on phosphorus

(i) *Hypoparathyroidism of encephalopathic origin* This is probably a form of hypoparathyroidism produced by a disturbance of the hypothalamic parathyroid connexions (hypothetical) Zondel in his text book recorded a case of an adolescent girl under his personal observation who developed latent tetany with low blood calcium under certain conditions of raised temperature and who had previously had encephalitis lethargica followed by other chronic sequelae Winer (1945) described tetany and convulsions with a serum calcium of 5 1 mg per 100 c c in a man of 41 who had sustained a head injury and in whom a ventriculogram showed dilatation of the third ventricle

(d) Clinical Picture

The major manifestations may be classified under six headings

(a) Paraesthesia and muscular spasms
(b) Convulsions
(c) Gastro intestinal disturbance
(d) Respiratory disturbances
(e) Psycho neurosis and psychosis
(f) Trophic disturbances

One or all of these manifestations may be met with and in latent tetany ectodermal trophic changes may be the only clinical manifestation

(a) *Paraesthesia and muscular spasms* The only disturbance in mild tetany may be numbness and tingling of the fingers A burning sensation sometimes occurs or the fingers may feel stiff Cramps of the calf muscles tend to be worse at night The muscles may be in a state of chronic tonic contraction and if the facial mu cles are so involved a characteristic facies develops e g mask like face with the corners of the mouth

drawn downwards and the nasolabial folds accentuated the forehead may be wrinkled and the eyes wide open Tonic muscular contractions are occasionally associated with violent unbearable pain

Fibrillary muscular twitchings may be localized to groups of muscles or widespread Gross muscular spasms are often very painful and the patient then cries out with pain and perturbation They last for minutes or hours and may occur many times a day Characteristically the muscles of the hands and feet are involved producing carpo pedal spasm The fingers are flexed at the metacarpo phalangeal joints and extended at the inter phalangeal joints while the thumb is flexed across the palm producing the obstetric hand The wrists and elbows may also be flexed bringing the hands across the body The toes are flexed the ankle joint extended and the sole of the foot inverted Facial and neck muscles are also involved in some patients

(b) *Convulsions* Epileptiform attacks both petit mal and grand mal are known to occur even in the absence of other signs and patients have been treated in neurological clinics for years as idiopathic epilepsy Kowallis (1941) describes an attack in a woman of 32 suffering from idiopathic hypoparathyroidism as follows

> Seizures commenced in the sixth post partum week and subsequently occurred every two weeks They were characterized by sudden onset without warning any time of the day or night There were loss of consciousness biting of the tongue clonic movements of all extremities and vesical incontinence *The seizure was followed by a deep sleep* The whole episode involved about an hour The patient was not conscious of what happened during the attacks although she remembered the residual headaches and mental depression After the onset of her convulsions definite personality changes developed primarily irritability stubbornness and forgetfulness

In this case the serum calcium was 5 1 mg per 100 c c and the phosphorus 4 8 mg In the case described by Himsworth and Maizels in a boy of 12 carpo pedal spasms or grand mal attacks occurred and were completely controlled by calciferol providing the serum calcium was not allowed to fall below 7 mg per 100 c c Grand mal attacks were even avoided above calcium levels of 5 5 mg per 100 c c An encephalogram may show characteristic changes in tetany Apart from headaches associated with epilepsy, typical migraine may be a manifestation of tetany

(c) *Gastro intestinal disorders* Spasm of the gastro intestinal musculature produces abdominal cramps pain and vomiting Laparotomy has been performed for suspected perforated gastro duodenal ulcer or appendicitis and in fact ileal spasm has produced a fatal ileus Spasm of bile passages produces a clinical picture of gall stone cholic and rarely even transitory jaundice

(d) *Respiratory disorders* Spasm of the larynx is liable to occur more especially in rickety children with spasmophilia The attacks are usually sudden in onset and alarming in their dramatic presentation Spasm of the bronchial musculature simulates bronchial asthma

(e) *Psycho neurosis and psychosis* Apart from changes in behaviour pattern as seen in Kowallis s case one meets with impaired memory and intellectual capacity mental instability anxiety and depression More rarely hallucinations confusion states manic depressive conditions paranoia schizoid personality and dementia are part of a chronic tetany Greene and Swanson (1941) record 5 cases of psychosis out of a total of 18 examples of parathyroid insufficiency They state that the psychosis is usually of a toxic delirious type occurring during the first few months of the parathyroid deficiency and may be the only manifestation With adequate treatment of the para thyroid insufficiency the prognosis is considered to be good although response may not be immediate

(f) *Trophic disturbances* These involve ectodermal tissue e g skin hair nails teeth and eye lenses are more frequently associated with the parathyroid form of tetany and are more chronic manifestations There is often a diffuse thinning of the hair and complete loss may occur in acute exacerbations of chronic tetany The nails show fraying brittleness grooving necrosis and detachment The teeth are defective in enamel and dental caries is frequent Teeth may fall out Lachman records various skin disorders impetigo herpetiformis pustules acrodermatitis psoriasis pustulosa psoriasis and chloasma Lenticular opacity has been produced after experimental para thyroidectomy and is by no means rare in chronic parathyroid deficiency although it is not found in other forms of tetany It may be obvious clinically or only detectable on special slit lamp examination In Himsworth and Maizels s boy with

congenital thyroid and parathyroid deficiency he presented himself at the age of 12 with bilateral cataracts

[Werner (1904) described a heredo familial disorder in which cataracts baldness greying of the hair and scleroderma occurred in childhood or adolescence The disorder might be associated with osteoporosis and metastatic calcification of vessels Oppenheimer and Kugel (1941) found a negative calcium balance in one patient but in two others it was normal In one autopsy the parathyroids were hyperplastic the adrenal cortex showed multiple adenomas the thyroid multiple colloid adenomas the testes atrophy and the pituitary apparent normality They stated that baldness was found in the second decade, scleroderma in the third and cataract in the fourth One of their patients had diabetes and two others hypoglycaemia]

(e) Diagnosis

This is not difficult in a well developed case and once made the detection of minor manifestations soon follows Trousseau s sign consists of producing a carpal spasm by maintaining a sphygmomanometer above the systolic pressure for 1 to 5 minutes Chvostek s sign is the production of contraction of facial muscles by tapping the facial nerve just below the zygoma and in front of the parotid gland Erb s sign is an exaggerated muscular contraction in response to minimal electrical stimuli

The serum calcium is nearly always below 8 mg per 100 c c but is normal in alkalosis though the ionized calcium is decreased The serum phosphorus is normal or raised in hypoparathyroidism but is below normal in steatorrhoea or rickets (normal phosphorus = 2 5 to 4 mg per 100 c c) Bleeding and coagulation times are prolonged owing to the low blood calcium Tetanus is of course in no way related to tetany and is an infective condition following a contaminated wound Opisthotonos does not occur in tetany (For a description of Werner s syndrome see previous paragraph on Trophic disturbances)

(f) Course and Prognosis

If an underlying disorder is recognized e g rickets or alkalosis cure should result Hypoparathyroidism can be controlled but in severe cases the borderline is easily crossed and intermittent attacks may occur

(g) Treatment

Acute attacks The immediate treatment is the slow intravenous injection of 10 or 20 c c of 10 per cent calcium chloride

or gluconate the chloride being theoretically preferable The gluconate has the advantage that it may also be injected intramuscularly Parathormone 20 units may be injected intravenously acting within 30 minutes or intramuscularly acting within a few hours It is only to be used as an emergency measure since a refractory state develops after repeated injections and it further demineralizes bones where osteitis fibrosa is already present In any case parathormone has no advantage over calcium The more immediate treatment is repeated as frequently as necessary and is followed as soon as possible by the more sustained treatment indicated below

Subacute or chronic tetany (a) *Calcium salts* The optimum calcium salt is calcium chloride because this salt is very soluble in water tends to produce a slightly acid reaction favouring absorption and because it furnishes the largest proportion of calcium per gm of salt (Severinghaus 1942) From the molecular weights it can be seen that 1 gm of the salts will produce the following amounts of the element calcium gluconate 93 mg lactate 185 mg chloride 360 mg The chief drawback to its use in oral preparations has been its highly astringent effect on the mouth and pharynx which can be minimized by giving it as a 25 per cent solution in a vehicle such as syrup of glycyrrhiza 2 to 4 drachms daily before meals However in practice calcium lactate or gluconate powder 12 gm a day (a table spoonful 3 or 4 times daily) is effective in the majority of cases The gluconate is more palatable and is soluble easily absorbed and slightly sweet Robertson (1941) found no benefit from the mild acidosis produced by ammonium chloride

(b) *Vitamin D (calciferol)* This is a most satisfactory form of therapy if given in adequate doses The anti rachitic dose is only 700 to 1 000 units a day but the dose required to raise a low serum calcium or to correct chronic tetany is 50 000 to 200 000 units daily and the larger doses are effective even in the absence of a large intake of calcium or a low phosphorus intake Since calciferol can be obtained in capsules of 100 000 units this form of therapy is the one of choice

(c) *Dihydrotachysterol (A T 10)* This substance was introduced by Holtz in 1933 It is a by product from the radiation of ergosterol separated from the vitamin D component by fractionation Although it has no true anti rachitic properties

congenital thyroid and parathyroid deficiency he presented himself at the age of 12 with bilateral cataracts

[Werner (1904) described a heredo familial disorder in which cataracts baldness greying of the hair and sclerodermia occurred in childhood or adolescence The disorder might be associated with osteoporosis and metastatic calcification of vessels Oppenheimer and Kugel (1941) found a negative calcium balance in one patient but in two others it was normal In one autopsy the parathyroids were hyperplastic the adrenal cortex showed multiple adenomas the thyroid multiple colloid adenomas the testes atrophy and the pituitary apparent normality They stated that baldness was found in the second decade, sclerodermia in the third and cataract in the fourth One of their patients had diabetes and two others hypoglycaemia]

(e) Diagnosis

This is not difficult in a well developed case and once made the detection of minor manifestations soon follows Trousseau s sign consists of producing a carpal spasm by maintaining a sphygmomanometer above the systolic pressure for 1 to 5 minutes Chvostek s sign is the production of contraction of facial muscles by tapping the facial nerve just below the zygoma and in front of the parotid gland Erb s sign is an exaggerated muscular contraction in response to minimal electrical stimuli

The serum calcium is nearly always below 8 mg per 100 c c but is normal in alkalosis though the ionized calcium is decreased The serum phosphorus is normal or raised in hypoparathyroidism but is below normal in steatorrhoea or rickets (normal phosphorus = 2 5 to 4 mg per 100 c c) Bleeding and coagulation times are prolonged owing to the low blood calcium Tetanus is of course in no way related to tetany and is an infective condition following a contaminated wound Opisthotonos does not occur in tetany (For a description of Werner s syndrome see previous paragraph on Trophic disturbances)

(f) Course and Prognosis

If an underlying disorder is recognized e g rickets or alkalosis cure should result Hypoparathyroidism can be controlled but in severe cases the borderline is easily crossed and intermittent attacks may occur

(g) Treatment

Acute attacks The immediate treatment is the slow intravenous injection of 10 or 20 c c of 10 per cent calcium chloride

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it is a very powerful agent for raising the serum calcium by increasing the absorption of calcium The urinary calcium is increased but the faecal calcium decreased (Rose and Sunderman 1939) As to its equivalent dosage compared with calciferol Severinghaus records that 1 mg of calciferol is equivalent to 40 000 international units of vitamin D or 0 2 mg of dihydrotachysterol which latter is contained in 0 1 c c of the commercial oily solution Therefore 0 25 c c of A T 10 corresponds to 100 000 units of vitamin D One commercial preparation is called Hytakerol Severinghaus suggests however that A T 10 is more toxic than calciferol and where large doses of either are being used control estimations of serum calcium must be periodically made Toxic symptoms caused by overdosage of either vitamin D or A T 10 may be nausea vomiting anorexia abdominal cramps vertigo tinnitus polyuria thirst and calcium deposition in the viscera especially calcinosis of the kidneys (cf hyperparathyroidism) It is probable that so called toxicity is a measure of the power of a given dose of calciferol or A T 10 to produce hypercalcaemia and is proportional to the degree of hypercalcaemia produced

The Sulkowitch reagent (oxalates) may be used as a rough urinary test an equal amount of reagent being added to the urine If the calcium is precipitated as a fine white powder of calcium oxalate the serum calcium is probably normal if no precipitate there is no calcium in the urine and the serum calcium is 5 to 7 5 mg per 100 c c if there is a heavy precipitate so that an appearance of milk is given the serum calcium is probably above 12 mg per 100 c c

(d) *Low phosphorus diets* These are definitely beneficial (Anderson and Lyall 1939) the desirable intake not being greater than 0 5 gm per day Shelling recorded this with Goodman in 1934 and stated that it meant eating less meat glands nuts, milk cheese and yolk of eggs and more fruit vegetables white of eggs carbohydrate and fat

Fallopian tubes Clinical studies also suggest that they are a major factor in determining behaviour pattern

It is an important principle in endocrinology that the giving of a hormone inhibits the corresponding pituitary stimulus e g thyroxine inhibits the secretion of the pituitary thyrotrophic hormone This is true both of oestradiol and testosterone It is also true and of great importance clinically that the giving of oestradiol to the male will produce an involution of the testis by suppressing the pituitary gonadotrophic stimulus the ultimate result being a physiological castration and that testosterone in the female will similarly put an end to all ovarian function quite apart from its more direct positive effects e g development of masculine hairiness and voice This castration effect in the male and female however is dependent upon a continual inhibition of the pituitary gonadotrophic stimulus by the continual administration of oestradiol or testosterone in adequate dosage and the cessation of such treatment permits the testis or ovary to resume its normal function There is some evidence that small doses or intermittent doses of oestradiol and testosterone may under certain circumstances act as a pituitary gonadotrophic stimulus

It is now known that the female as well as the male secretes androgens from the adrenal cortex and both sexes secrete oestrogens and progesterone from this source It is not generally recognized that the ovary itself may secrete androgens Thus Hill (1937) grafted ovaries into the ears of castrated mice and found that normal growth and secretion of the seminal vesicles and prostate occurred an effect which did not result from oestradiol or progesterone This makes it easier to understand why certain ovarian tumours (arrhenoblastoma) produce virilism (masculinization) in women Certain androgens produce growth of the vagina uterus and mammary ducts and progestational proliferation of the rabbit s uterus It is perhaps astonishing that the testis of the horse is rich in oestrogens and stallions have enormous amounts of oestrone in the urine (Zondek)

THE TESTIS

There are two essential components of the testis the seminiferous tubules which produce spermatozoa and the interstitial

SECTION FIVE

THE GONADS

A PHYSIOLOGY

CHAPTER XXXIII

INTRODUCTION

THE fact that the references to this section include three large books on the physiology and chemistry of the gonads indicates that this section can deal only briefly with the more important physiological essentials paying attention to those aspects which have a more direct bearing on the clinical approach

The activity of the testis and ovary is dependent upon the activity of the pituitary (or hypothalamic pituitary system) and hypophysectomy prevents the development of the gonads (testis and ovary) in the immature young animal (before puberty) or produces involution of the gonads in the adult animal These inhibitory effects of hypophysectomy may be prevented or repaired by the injection of pituitary extracts (gonadotrophins) in smaller mammals although in man this statement is only partially true owing to the present incomplete solution of the biochemical problems involved Pituitary gonadotrophins may also accelerate sexual maturity in young animals and this may happen spontaneously in man as well as experimentally in smaller animals

Endocrine glands other than the testis ovary and pituitary may influence sexual function This is especially true of the adrenal cortex which secretes adrenosterone (similar to testosterone) oestradiol and progesterone and of the thyroid gland the excessive or deficient secretion of thyroxine influencing the pituitary secretion of gonadotrophins

The testis secretes testosterone and the ovary secretes oestradiol and progesterone These hormones are responsible for the development of differential secondary characteristics at puberty e g skeletal muscular strength hair breasts voice and possibly fat deposition as well as for the more obvious influence on the penis prostate seminal vesicles uterus and

epithelium and colloid storage The increased growth of long bones is inconstant The spontaneous activity of the castrated rat is less than that of the normal rat Castration has an important effect on the anterior pituitary gland causing an increase in its gonadotrophic potency an increase in its size and weight and the appearance of vacuolated castration cells which are believed to be basophilic in character (although in some species some observers have noted eosinophilic staining) It is also probable that there is an increased secretion of pituitary adrenocorticotrophic hormone since the adrenal cortex undergoes hyperplasia and the inner androgenic or X zone which normally disappears in the male mouse at puberty persists and enlarges or reappears if castration occurs after puberty (see Adrenal section) In cockerels castration leads to atrophy of the comb and the regrowth of the comb after injections of adrogens is the older method of assay of androgens by comb growth measurement

TESTOSTERONE

Berthold restored capons (castrated cockerels) atrophic combs by testis implantation as early as 1849 and Pezard obtained similar results by injecting a fine testicular suspension in 1911 McGee (1927) working in Koch s laboratory first obtained similar results with a true chemical extract of bulls testes This work was put on a sound quantitative basis by Gallagher and Koch (1930) They defined the capon unit (c u) as the amount of substance which when administered to each of three capons on two successive days produces in the course of the third or fourth day an average increase of 20 per cent in the area of the comb (measured on a shadowgraph by a planimeter) Butenandt (1931) was the first to isolate a chemical substance with androgenic properties As the testis contained only minute amounts he used the urine of healthy men and obtained 15 mg of the hormone from 15 000 litres of urine He found the substance to be a sterol like ketone and named it androsterone (Gr *andro* = male) Butenandt correctly forecast its formula to be $C_{19}H_{30}O_2$ Ruzicka (1934) confirmed this formula and synthesized androsterone from dihydrocholesterol He also showed that 60 micrograms (μ g) of androsterone has the biological action corresponding to 1 capon unit Another

cells of Leydig which secrete the essential male hormone testosterone Although as seen experimentally the activity of the seminiferous tubules is dependent directly or indirectly upon testosterone secretion the functioning of the interstitial cells and the secretion of testosterone are in no way dependent upon the seminiferous tubules This is also found to be the case clinically when primary and secondary sexual characteristics may be completely normal in a sterile man (who secretes urinary androgens in normal quantities) and in whom biopsy may show destruction and hyalinization of the seminiferous tubules but *normal interstitial cells* The *seminiferous tubules are much* more sensitive to heat and to toxins than are the interstitial cells Thus in cryptorchism (testis retained in abdomen) the *seminiferous tubules are destroyed* but the *interstitial cells are* intact and function normally similarly when orchitis occurs as a complication of mumps usually only the seminiferous *tubules tend to be harmed* with resulting sterility in an *other* wise virile man (Some indirect experiments suggest that the seminiferous tubules secrete a hormone inhibin which inhibits pituitary gonadotrophic activity but in the present state of uncertain knowledge the writer proposes to ignore these experiments for the time being as they do not fit in with clinical observation)

Castration in man will be considered in the clinical section In smaller mammals e g rat dog &c prepubertal castration prevents development of the penis prostate and seminal vesicles and regression of these organs follows post pubertal castration Similarly libido and potency are lost There are however some apparent exceptions to these generalities particularly noticeable in some species Thus castrated male pigs will mount females in heat and rats will continue to do so for several months after castration Female pigs however will mount females in heat The penis although usually dependent upon the presence of the testes for its growth will in the pre pubertal castrated gelding attain almost the same size as that of the stallion Korenchevsky (1925) found that only 60 per cent of castrated dogs became fat indicating that increased adiposity depends upon a genetic as well as a hormone factor A decrease in basal metabolism is found in some species and may be asso ciated with involutional changes in the thyroid low cuboidal

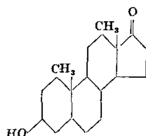
progestational changes in the endometrium The latter action is very weak compared with progesterone and is quite ineffective in the monkey Testosterone also acts synergistically with oestrone and both administered simultaneously to ovariectomized rats lead to a greater development of the uterus and vagina than either separately (Korenchevsky 1937) but testosterone can prevent the vaginal cornification produced by oestradiol in the mouse In the monkey 7 mg testosterone propionate per day completely inhibits menstrual bleeding and endometrial changes (Zuckerman 1937 and Papanicolaou 1939)

THE OVARY

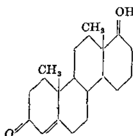
The general effects of bilateral ovariectomy and the resultant changes in other endocrine glands are similar to those following castration in the male (see previous section) More specifically the uterus Fallopian tubes and vagina remain infantile in the immature animal or involute in the adult animal and the oestrous or menstrual cycle ceases also the mammary glands undergo atresia involving both ducts and alveoli

The menstrual cycle in woman is determined by the secretions of the ovary which in its turn undergoes a cyclical monthly series of changes dependent upon the activity of the pituitary What determines the monthly rhythm of the pituitary secretions is unknown in mammals but in birds seasonal activity depends upon the action of light on the retina and nervous impulses transmitted to and via the hypothalamic pituitary mechanism The initial phase of the monthly cycle is characterized by growth of the Graafian follicle and associated secretion of oestradiol with a resultant action of the latter on the uterus resulting in proliferation of the uterine endometrium (proliferative phase) About the fourteenth day of the cycle (which is usually counted from the first day of menstruation) ovulation occurs (tenth to seventeenth day varying individually but tending to be constant for any one individual) oestradiol continues to be secreted but in addition with the conversion of the ruptured Graafian follicle into a corpus luteum progesterone is secreted in the latter half of the cycle Progesterone acting upon the proliferative uterine endothelium converts it into a secretory type of endothelium (secretory phase) with enlarged tortuous glands lined by columnar cells containing glycogen Changes take place in the

androgenic substance obtained from the urine was dehydroiso androsterone This hormone is particularly interesting because it is intermediate in degree of unsaturation between androsterone and oestrone Thus the close chemical relationship between the androgens and the oestrogens is evident The androgenic effect of androsterone on the prostate seminal vesicles and penis of castrated rats was observed by Korenchevsky Dennison and *Simpson (1935) However androsterone had a relatively weak* effect on these organs compared with its effect on the capons comb or with that of an equal quantity of testicular extract standardized in capon units and this discrepancy indicated that androsterone was not the essential testicular hormone In June 1935 David Dingemanse Freud and Laqueur reported the isolation of testosterone obtaining 10 mg of the hormone from 100 kg of testis tissue and Laqueur found that testosterone is ten times as powerful as androsterone in promoting comb growth the capon unit being contained in about 10 micrograms of the material Androsterone is thus seen to be a relatively weak urinary transformation product of the testicular hormone testosterone which is Δ^4 androsterol 17 one 3



Androsterone
$C_{19}H_{30}O_2$



Testosterone
$C_{19}H_{\ 8}O$

Testosterone can repair qualitatively and quantitatively all the effects of castration in the mammal

Testosterone and other androgens however have interesting effects on the female Thus it produces enlargement of the clitoris and growth of the peri urethral glands which are normally atrophic and which represent the rudimentary female prostate In ovariectomized rats testosterone produces growth of the vagina and mucification of the vaginal epithelium as in pregnancy there is also marked growth of the uterus with

extract or material which just sufficed to produce a positive or oestrous response in the castrated mouse The rat unit is about four times the amount of the mouse unit and different laboratories gave different relative values The isolation of pure oestrone and later oestradiol permitted standardization in the unvarying terminology of milligrams The international unit of oestrone is 0 1 microgram or 0 0001 mg of pure oestrone powder This is found to be roughly equivalent to 1 mouse unit or ¼ rat unit but biological equivalents vary according to the laboratory technique and species of animal The Allen–Doisy test proved to be an indispensable guide in the search for a pure oestrone producing hormone the other outstanding preliminary step being the important discovery by Ascheim and Zondek (1927) that an oestrous producing substance is excreted in considerable quantities in the urine of pregnant women

ISOLATION OF OESTRONE

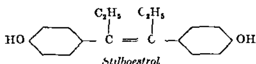
In 1929 Doisy and co workers at the St Louis University School of Medicine and Butenandt at Gottingen isolated a crystalline oestrogenic substance oestrone $C_{18}H_{22}O_2$ from the urine of pregnant women and a few months later Lacqueur and colleagues had a similar success Although oestrone was the name finally agreed upon to indicate the ketonic character of the hormone the following original names or synonyms still confuse the literature although given up by their originators theelin (Doisy) oestrin (Parkes) keto hydroxy oestrin (Marrian) menformon (Lacqueur) folliculin (Girard) An effort to obtain international nomenclature was made by Adam and colleagues in 1933 when the term oestrone was agreed upon An alcohol resulting from its reduction was called oestradiol and another derivative having three hydroxyl groups was called oestriol The term oestrin is used to indicate the entire group of oestrogenic substances found in urinary or tissue extracts but in view of the above confusion in nomenclature it seems advisable to drop this term altogether and to use the word oestrogens as a collective term denoting oestrogenic activity when tested biologically

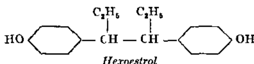
The international unit of oestrone is 0 1 microgram (i e 0 1 μg = 0 1γ = 1×10^{-7} g) of the standard substance kept at

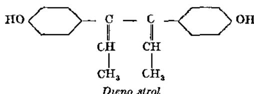
breast and will be considered separately If the ovum which has passed from the ruptured Graafian follicle down the Fallopian tube and ultimately to the uterus has remained unfertilized the corpus luteum disintegrates on the twenty eighth day (average), and there is a sharp fall in both oestradiol and progesterone secretion with resulting disintegration and shedding of the uterine mucous membrane (menstruation) The cycle then repeats itself The concentration of oestradiol in the blood has two peaks just before ovulation and just before menstruation Experimental studies in monkeys show that the rapid fall of oestradiol concentration determines the onset of menstruation and that this can be made to occur experimentally by giving oestradiol to an ovariectomized monkey and then ceasing its administration This is known as withdrawal bleed ing and occurs from a proliferative endometrium It is there fore an anovulatory menstruation which is met with naturally in some monkeys and which may occur in women being one of the causes of sterility It is diagnosed by biopsy of the endo metrium If in the above experiments following cessation of oestradiol administration progesterone is given bleeding is delayed and may not take place until the progesterone injections cease This is an experimental production of menstruation from a secretory type of endometrium as is met with normally in women who ovulate (Zuckerman 1937) Kaufmann (1932) pro duced similar changes by oestradiol and progesterone in an ovariectomized woman

As in other branches of endocrinology an accurate under standing of the mechanism of sex function followed the extrac tion isolation and synthesis of the ovarian hormones and the study of their biological effects in experimental animals as well as in man Chemists were dependent upon the earlier work of biolo gists for biological methods of assay Thus in 1923 Allen and Doisy found that a typical oestrous vaginal reaction which occurs every 4 to 6 days in the mouse (and rat) could be pro duced in ovariectomized animals by injecting ovarian chemical extracts A positive reaction is the presence of cornified non nucleated vaginal epithelium cells, with few or no polymorpho nuclear cells and a negative reaction by some nucleated vaginal cells and a preponderance of polymorphonuclear cells A mouse unit of the hormone was defined as the quantity of oestrogenic

to the synthesis of stilboestrol Originally attempting to obtain a substance the structure of which was similar to that of the natural oestrogens they obtained a series of oestrogenic compounds all containing the phenanthrene nucleus A further series of synthetic oestrogens bore little resemblance in structure to oestrone Joining forces with Sir Robert Robinson Cook and Dodds produced three substances now extensively used in medicine namely stilboestrol (diethyl stilboestrol) hexoestrol and dienoestrol Of these substances Dodds writes they are all more powerful than the naturally occurring hormone yet bear only a superficial resemblance to its structure Their formulae are


Stilboestrol


Hexoestrol


Dienoestrol

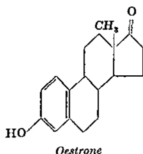
These synthetic hormones have more than twice the quantitative activity of oestrone or oestradiol and of greater importance are as active by mouth as by injection whereas the natural oestrogens have only one fifth or less activity by mouth as compared with injection

(b) Toxicity of Stilboestrol

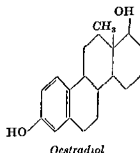
Stilboestrol and similar compounds were found to produce unpleasant symptoms in some women e g nausea vomiting and abdominal cramps and at one time were rejected in America as being unsuitable for therapy for this reason and because of alleged toxicity based on animal experiments However they

the National Institute for Medical Research, London A litre of pregnant women s urine yields only about 1 mg of oestrone but in 1930 Zondek discovered that pregnant mares urine yielded ten times as much per litre Zondek (1934) made the further astonishing discovery that the testes of the horse is the richest tissue known containing oestrogenic hormone its yield being 300 times that of the mare s ovary and that the urine of the stallion yields twice as much oestrogenic material as that of the pregnant mare The figures given by Zondek of oestrogenic content of 1 litre of urine in mouse units are striking woman 70 pregnant woman 10 000, mare 200, pregnant mare 100 000 stallion 170 000 This paradox of nature is true only of the equines (horse zebra ass kiang) but not of bulls monkeys or man Oestrone has also been obtained from plants and flowers

For details of the brilliant clinical work leading to the preparation of the dihydro compound oestradiol from oestrone (Shwenck and Hildebrandt) the reader is referred to Fieser s informative book on the Sterols The fact that oestradiol was four times as potent as oestrone led to Doisy s (1935) successful attempts to extract it from the hog s ovary and to the recognition that oestradiol was the natural hormone secreted by the ovary and oestrone a urinary degradation product



Oestrone



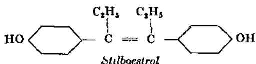
Oestradiol

SYNTHETIC OESTROGENS

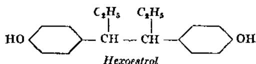
(a) Stilboestrol

Before the structure of oestrone was established and it was only known with certainty that the oestrous producing hormone was a hydroxy *ketone containing a reduced phenanthrene* nucleus Cook and Dodds (1933) began an investigation that led

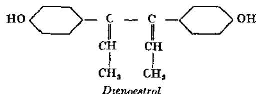
to the synthesis of stilboestrol Originally attempting to obtain a substance the structure of which was similar to that of the natural oestrogens they obtained a series of oestrogenic compounds all containing the phenanthrene nucleus A further series of synthetic oestrogens bore little resemblance in structure to oestrone Joining forces with Sir Robert Robinson Cook and Dodds produced three substances now extensively used in medicine namely stilboestrol (diethyl stilboestrol) hexoestrol and dienoestrol Of these substances Dodds writes they are all more powerful than *the naturally occurring hormone yet bear* only a superficial resemblance to its structure Their formulae are



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These synthetic hormones have more than twice the quantitative activity of oestrone or oestradiol and of greater importance are as active by mouth as by injection whereas the natural oestrogens have only one fifth or less activity by mouth as compared with injection

(b) Toxicity of Stilboestrol

Stilboestrol and similar compounds were found to produce unpleasant symptoms in some women e g nausea vomiting and abdominal cramps and at one time were rejected in America as being unsuitable for therapy for this reason and because of alleged toxicity based on animal experiments However they

are now widely used clinically. Dodds believes that the unpleasant symptoms are not toxic but associated with their oestrogenic potency and that the nausea and vomiting are comparable to similar symptoms in early pregnancy when the body is flooded with natural oestrogens. The writer thinks this view is rather too sanguine as sensitive patients have such symptoms even with very small doses. However, excluding some 10 per cent of sensitive patients, many years clinical experience has not confirmed the earlier prognostications of serious long term toxic effect from the continuous administration of stilboestrol. The same is true of a predicted carcinogenic effect in women. Nevertheless, animal experiments, both as to toxicity and carcinogenic effect, will be described briefly so that their possible significance will not be ignored.

Zondek and colleagues (1943) showed that stilboestrol is inactivated by the liver *in vitro* but much less rapidly than is oestrone. He considers that this finding explains the greater oral efficiency and the toxic side effects of stilboestrol in man. Page Russell and colleagues (1941) found that stilboestrol was not toxic to rats when fed by stomach tube in doses five times the average human therapeutic dose. When, however, the dosage was increased to 25 times the therapeutic dose, there resulted among 49 rats haemorrhagic gastric mucosa in 1, ulcer of oesophagus in 1, haemorrhage into the adrenals in 1, and cloudy swelling of the kidneys in 4. In a further series of 11 animals which received 500 times the therapeutic dose there was found liver damage in 2, adrenal haemorrhage in 3, cloudy swelling of the kidneys in 2, gastritis in 1, and hypoplasia of the bone marrow, leucopenia, neutropenia and thrombocytopenia in 2 animals.

The possible carcinogenic action of stilboestrol in mice will be discussed elsewhere, but it appears that both the natural oestrogens and stilboestrol will produce an increased incidence of mammary cancer in certain strains of ovariectomized mice and of male mice if given over a prolonged period. There is, however, a further point of association between oestrogenic activity, namely, that carcinogenic hydrocarbons may be slightly modified without losing their carcinogenic potentialities so as to develop oestrogenic properties (Dodds and others 1941).

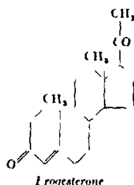
PROGESTERONE

Progesterone is the hormone secreted by the corpus luteum of the ovary It produces a secretory phase of the uterine endometrium in preparation for the nidation of the ovum inhibits uterine motility suppresses ovulation and induces mammary alveolar development The international unit is the specific progestational activity of 1 mg of crystalline progesterone Prior to the isolation of pure progesterone corpus luteum extracts were tested on rabbits The Corner–Allen rabbit unit is the minimal amount of an extract which given in five daily doses subcutaneously to a 3 to 4 kg rabbit spayed 18 hours after coition will produce in the uterus a progestational proliferation similar to that of the eighth day of pregnancy One milligram of progesterone is approximately equivalent to a Corner–Allen unit A modification of the latter test is to sensitize a young rabbit with oestradiol and then test for progestational effect with the corpus luteum extract (Clauberg 1933) Progesterone has no action on the endometrium of the uterus unless it has been previously sensitized by oestrogens

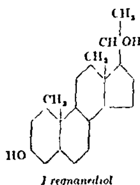
As long ago as 1903 Fraenkel showed that removal of the corpus luteum of a rabbit after ovulation prevented or terminated pregnancy but it was not until 1928 that Corner and Allen proved that these adverse effects did not follow if an extract of corpus luteum was injected

Both W M Allen (1932) and F L Hisaw (1932) obtained very active but crude crystallizates of the corpus luteum and two years later Butenandt and soon after Allen and Wintersteiner isolated an unsaturated diketone progesterone $C_{21}H_{30}O_2$ (The name progestin was given to Allen s earlier extracts and is best discarded) Butenandt later synthesized progesterone from stigmasterol which may be obtained from soya bean Progesterone has been detected in the placenta in pregnancy urine and in the adrenal cortex but the most fruitful source for extraction purposes was found to be the sow s ovary Even so the difficulty of the task of the earlier investigators is shown by the fact that 10 sows are required to produce enough hormone to cause the characteristic physiological changes in the uterus of a single rabbit Progesterone is excreted in the urine as an inactive hydrate pregnanediol glucuronidate

Progesterone is inactive when given by mouth but a derivative of progesterone known as anhydro hydroxy progesterone or pregnenninolone or ethinyl testosterone or ethisterone is active by mouth This activity however is only about a fourth of that of injected progesterone and there is some evidence of a qualitative difference It is of interest that both testosterone and *desoxycorticosterone (see Adrenal section)* have a slight progestational activity It is al o noteworthy that anhydro hydroxy progesterone (ethisterone) in addition to its progesterone like activity also has an androgenic and oestrogenic effect (Emmens and Parkes 1939)



Progesterone



Pregnanediol

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INHIBITION OF THE PITUITARY GLAND BY SEX HORMONES

(a) Oestrogens

I have indicated previously that it is justifiable to lay down the following important law in endocrinology the administration of any hormone will inhibit the secretion of the corresponding hormone of the pituitary gland which normally gives rise to its production e g thyroxin inhibits the secretion of thyrotrophic hormone oestradiol of gonadotrophic hormone

Although previous investigators had demonstrated the basis for such a law in regard to the oestrogens it was not until 1936

that Cramer and Horning in London and Zondek in Jerusalem showed that oestrogens in mice and rats administered over many months even in small doses produced large haemorrhagic chromophobe adenomas of the anterior pituitary gland as well as the resulting atrophy of testes and ovaries Both groups of investigators pointed out that these changes however extended beyond the sex glands Thus Cramer and Horning found that there was failure of growth complete disappearance of fat atrophy of the spleen and thymus extensive degenerative changes in the adrenal cortex active adrenaline secretion by the adrenal medulla and hypertrophy of the islets of Langerhans Zondek observed extreme dwarfism with failure of epiphyses to unite and enlargement of the adrenal glands The dwarfism responded to Evans's pituitary growth hormone showing that the oestrogens had inhibited the secretion of the animal's own pituitary growth hormone It would thus appear that if the dose of administered hormone is large enough or given over a long enough period the inhibitory effect on the pituitary gland spreads and involves other functions but the specific gonadotrophic inhibition is the first to be obtained

Of the effect on the sex organs Zondek states The scrotal sac vanishes completely the penis becomes small the testes remain infantile and formation of spermatozoa is completely inhibited seminal tubules and prostate are atrophic in females the ovaries are so small that they cannot be recognized with the naked eye They contain only small follicles but never corpora lutea (To complicate the general law it appears that oestrogens injected over a short period in appropriate dosage may release a pituitary luteinizing hormone and thus produce corpora lutea even though the pituitary chromophil cells show commencing degranulation (Selye Collip and Thomson 1935 Wolfe and Wright 1938))

Noble (1938) found that synthetic oestrogens e g stilboestrol inhibited the pituitary in similar manner to natural oestrogens and the pituitary gland showed an absence of gonadotrophic hormone Deanesly (1939) found similar changes in the rat after implantation of oestrone and oestradiol tablets for from 10 to 270 days With regard to the histology of the pituitary she confirms and extends the findings of Severinghaus (1937) stating that

The early response consists of a degranulation of some of the basophil cells, later they enlarge and their Golgi apparatus hypertrophies. With continued oestrogen therapy there is wide spread degranulation and enlargement not only of the basophils but also of the acidophils; the chromophobe cells increase in relative numbers owing to the degranulation and also absolutely owing to mitotic division. After prolonged oestrogen administration the pituitary gland has a uniform chromophobe appearance, the cells being swollen and having distinct cell boundaries and no granules. Part of the enlargement is due to marked vascular congestion. In the anterior lobe there is much colloid accumulation and large areas of degenerating cells. In some cases the centre of the lateral areas of the anterior lobe consists of extravasated blood and degenerating cells.

Even at this stage the changes were reversible since removal of the oestrone tablets lead to a return to a normal pituitary structure within 50 days. Rowlands and Sharpey Schafer (1940) showed that oestradiol diminished the urinary gonadotrophins of menopausal women and the gonadotrophin potency of pituitary glands of women between 54 and 70 years of age who came to autopsy with incurable disease.

(b) Progesterone

There is considerable evidence that progesterone inhibits pituitary activity. Loeb (1914) and Papanicolaou (1920) found that removal of the corpus luteum of the guinea pig led to ovulation and premature oestrous, and Papanicolaou (1926) obtained a lipoid extract of corpora lutea that inhibited oestrous and ovulation in the guinea pig. Corner (1935) prevented menstrual bleeding in monkeys by 1 mg. of progesterone daily and noted that bleeding followed in 6 days after the last injection of progesterone. Selye, Brown and Collip (1936) prevented the oestrous cycle of rats by progesterone. Phillip (1930) found that the pituitaries of women dying late in pregnancy had no gonadotrophic potency when extracted and tested biologically. Burrows (1939) found that progesterone produced hypospadias in female rats and prevented descent of the testis in male rats. Charipper as early as 1934 observed that a lipoidal extract of corpus luteum produced "pregnancy cells" in the pituitary gland of female rats—large ovoid cells with a deeply eosin stained homogeneous cytoplasm surrounding an eccentrically placed vesicular nucleus.

(c) Testosterone

Wolfe and Hamilton (1937) found that testosterone in rats led to degranulation of the majority of the pituitary basophil cells Wainman Reese and Koneff (1942) confirmed this but also noted vacuolated basophils and an increase in size and number of eosinophils Greene and Burrill (1940) found that low doses of testosterone 0 1 mg daily for 20 days in rats caused inhibition of testicular growth but that recovery followed cessation of treatment Korenchevsky and Hall (1939) pointed out that under the conditions of their experiments small doses of testosterone were paradoxically more injurious than larger doses Wells (1943) using the male ground squirrel demonstrated an inhibition of pituitary gonadotrophic hormone of such specificity that it involved only the I C S H (interstitial cell stimulating hormone) The interstitial cells of Leydig were severely injured whereas the seminiferous tubules in these short term experiments of 20 days were intact and spermatozoa formation was normal This is the best example of the specificity inhibition law postulated above Atrophy of the ovaries and uterine endometrium is another constant result of testosterone inhibition of the pituitary gland in female rats

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GONADOTROPHIC HORMONES

Hypophysectomy results in the involution of sex organs and pituitary implants have the power of completely restoring sex function in the hypophysectomized animal (male or female) The initial fundamental work in this field was carried out by Zondek and Ascheim (1927) and Smith and Engle (1927) Smith obtained cell free pituitary extracts with gonadotrophic potency and Ascheim and Zondek discovered that the urine of pregnant women contained gonadotrophic substances These latter are manufactured by the placenta and are therefore called chorionic gonadotrophins

Gonadotrophins were classified into two main classes by Ascheim and Zondek —Prolan A and Prolan B Prolan A produces ovarian follicle growth and Prolan B produces luteinization of the ruptured follicle Prolan A also produces stimulation of the spermatic tubules of the testes and Prolan B stimulation of the interstitial cells Prolan A is also called F S H (follicle stimulating hormone) and Prolan B is also known as L H (luteinizing hormone) When considering its action on the testis Prolan B is termed I C S H (interstitial cell stimulating factor) Prolan A and Prolan B are both present in the anterior pituitary gland Prolan A is also found in pregnant mare s serum and in the urine of male and female castrates or at the climacteric Prolan B is found in pregnant women s urine The evidence for the separate existence of these hormones is the ineffectiveness of chorionic gonadotrophins (pregnancy urine) in hypophysectomized animals compared with pituitary gland extracts The fact that the biological action varies with the age and species of animals and with the frequency or route of administration of the hormone has thrown some doubt on the existence of two separate hormones Nevertheless for all practical purposes Prolan A (F S H) and Prolan B (L H) appear to be separate hormones although it is more prudent to state that the action of a given

(c) Testosterone

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is the finding of an ovum (or ova) in a Fallopian tube by serial sections and Rowlands and Williams (1943) have used this technique in studying ovulation in hypophysectomized rats Where multiple or super ovulation was induced it could be recognized by the naked eye the segment of Fallopian tube containing the ova being swollen and translucent

The hypophysectomized animal is the ideal one for these experiments since in normal animals it is difficult to differentiate between the action of the animal's own pituitary gland and of the injected gonadotrophin In 1933 Leonard and Smith showed that in hypophysectomized rats post menopausal urine and pregnant mare's serum (F S H) produced growth of the follicle but that ovulation did not occur unless chorionic gonadotrophin (L H) was subsequently injected The latter hormone however was without effect unless preceded by F S H Rowlands and Williams (1943) confirmed and extended this work and found that a single injection of serum gonadotrophin is sufficient to prepare the ovaries for ovulation by L H (pituitary or chorionic) Serum gonadotrophin is long acting a single injection being as effective as five daily injections Chorionic gonadotrophin has however a brief action and is rapidly destroyed They found ruptured follicles in the ovaries 12 hours after the injection of chorionic gonadotrophins and ova in the tubes 1 hour after this Rowlands and Williams found that the phase of follicular growth during which a luteinizing stimulus has a maximum effect is very short Thus if F S H and L H are given together no luteinization occurred if L H was given 1 to 3 days after F S H a premature luteinization of the membrana granulosa prevented the escape of the ovum if the time interval was beyond 4 days in the rat only a proportion of rats ovulated They conclude from their experiment that ovulation is caused by an increase in concentration of luteinizing hormone at a particular phase of follicular growth Williams (1943) found that stilboestrol prevented atrophy of the ovaries following hypophysectomy and rendered them responsive to an ovulating stimulus without a preliminary preparation with F S H

The question whether gonadotrophins are effective in producing ovulation in woman is obviously important especially in cases of amenorrhoea menorrhagia and sterility Clinical therapeutic evidence is inconsistent and on the whole disappointing

extract (pituitary urine or serum) is predominatingly follicle stimulating or predominatingly luteinizing under the conditions of the experiment Both types of gonadotrophic hormone are however *undifferentiated as to sex the end result of their* activity depending on whether they *are injected into a male* or female animal and not on whether they *are obtained from* a male or female animal Thus *pituitary gland of the male or* female contains F S H and L H the urine of *pregnant women* contains L H and that of pregnant *mare's serum* F S H F S H acts on the seminiferous tubules and L H on the interstitial cells of Leydig whatever the source of the F S H and L H Prolan B (and sometimes A also) is found in the urine in degenerative conditions of the placenta (hydatid mole and chorionic epithelioma) and in some malignant testicular tumours

Zondek (1944) defines 1 rat or mouse unit of Prolan A as *the amount* sufficient to induce maturation of the follicles and *secondary cornification* of the vagina (1 mouse unit equals 4 rat units) One mouse unit of *Prolan B is defined as the* amount sufficient to change at least 1 *Graafian follicle* into a corpus luteum Although the gonadotrophins have not been isolated or synthesized standard concentrated powders have been prepared by the National Institute of Medical Research in London One international unit of gonadotrophic substance is said to be represented by 0 1 mg of the standard powder which *corresponds to 3 rat* units of Prolan A or of Prolan B

(a) Ovulation

The normal physiological process in a *menstrual* cycle is growth of the Graafian follicle rupture of the follicle and passage of the ovum into the Fallopian tube (ovulation) and then luteinization of the ruptured follicle (corpus luteum formation) Although the formation of a corpus luteum is usually taken as an *indication of a preceding ovulation this is not always the case* and luteinization of a follicle can be induced *without ovulation* having occurred For this reason a separate ovulating hormone has been postulated (Leonard 1931) but more probably this potency lies in the luteinizing hormone (L H) providing that its action is preceded for a sufficient period of maturation by the follicle stimulating hormone (F S H) The true test of ovulation

(b) The Effect of Gonadotrophins in the Male

Hypophysectomy in the rat and monkey is followed by disintegration of the seminiferous tubules cessation of spermatogenesis and involution of the interstitial cells of Leydig the latter resulting in atrophy of the penis prostate and seminal vesicles In the hypophysectomized rat while it is true that F S H will produce regeneration of the seminal vesicles and L H will stimulate the interstitial cells to normal activity biological tests do not reveal such a clear division of activity as might be conjectured if F S H and L H represented two distinct hormones or alternatively if the extracts contained only one hormone and not a proportion of the others According to some observers however L H is essential for effective interstitial cell stimulation (Van Dyke 1939 Pullen and others 1942) If there is a long latent period between hypophysectomy and treatment with gonadotrophins the latter are ineffective (Leathem 1941) In the hypophysectomized monkey L H has no influence on the seminiferous tubules but F S does produce some degree of repair (Smith 1942) The repair was evidenced by mitosis in the spermatogonia and the appearance of a few spermatocytes but did not extend to the formation of spermatids or sperm Further after a period of 20 days although injections were continued improvement was not maintained and ultimately regression occurred This is due to the production of gonadotrophin antibodies in the monkey s serum which inactivate the injected substance This antigonadotrophic activity decreased 30 days after leaving off the injections and disappeared after 60 days (Meyer and Wolfe 1939)

The evidence in man will be considered clinically but it may be summarized in the statement that whereas L H is effective in stimulating the interstitial cells with a secondary hypertrophy of testis and seminal vesicles resulting from increased secretion of testosterone both L H and F S H are ineffective or only incompletely effective in their action on the seminiferous tubules Experimentally testosterone will maintain or restore in some degree the structure and function of the seminiferous tubules in hypophysectomized rats and monkeys (Smith 1942) and some clinicians have recorded a beneficial influence on the seminal fluid in relatively infertile men

This is not surprising because quite apart from the actual gonadotrophic potency we have seen from the above experiments how important are such factors as dosage route of administration timing of administration and state of preparation of the ovary for an ovulatory stimulus Experiments on women have been carried out in those subjects who have had to undergo laparotomy for an abdominal condition necessitating surgery Some have been menstruating normally and others have suffered from amenorrhoea Initial experiments using intramuscular injections of pituitary extracts pregnancy urine extracts and pregnant mare s serum extracts were inconstant and on the whole it seemed impossible to produce ovulation and true corpus luteum formation Thus Watson Smith and Kurzrok (1938) found that serum gonadotrophin injected intramuscularly led to development of the follicles with cystic enlargement and luteinization of the theca but no ovulation Davis and Koff (1938) found that an intravenous injection of pregnant mare s serum gonadotrophin (F S H) led to the formation of young corpora lutea in 16 out of 36 women when their ovaries were inspected 16 hours later These were found at times in the menstrual cycle when they would not normally be present The disadvantage of the intravenous route is that gonadotrophins are impure substances and in sensitive patients may produce dangerous and even fatal allergic protein like reactions The same is less true but not unknown in using the intramuscular route This is not surprising as the therapeutic substances are derived from other species sheep bovine and pregnant mares The gonadotrophins from pregnant women s urine (L H) unfortunately do not produce ovulation or luteinization when injected in women However Rydberg and Pedersen Bjergaard (1943) found that if 3 000 international units of pregnant mare s serum gonadotrophin (F S H) were injected intramuscularly on the fourth to the ninth day of the menstrual cycle followed by intramuscular injections of human pregnancy urine gonadotrophin (L H) 1 500 units every other day for three injections in women suffering from amenorrhoea ovulation and corpus luteum formation occurred in the majority of patients so treated Their evidence was based on laparotomies pregnanediol urinary excretion and endometrial biopsies showing progestational proliferation

follicles but temporary or prolonged failure of corpus luteum formation (Williams Phelps and Burch 1941) In the male rat thyroidectomy produces a decrease in size of the prostate and seminal vesicles and a decrease in sperm production (Smelser 1939)

Chu (1944) found that thyroidectomy in the rabbit is followed by an increase in the number of follicles in the ovary and a decrease in the luteinizing potency of the pituitary gland and further that mating in such rabbits was not followed by ovulation as in normal rabbits Further thyroid extract given to thyroidectomized rabbits may suppress follicle formation and even produce ovarian atrophy Ovarian inhibition produced by large doses of oestradiol in normal animals is not effective in thyroidectomized animals (Chu and Lee 1945) Engle (1944) observed that thyroidectomy in monkeys led to amenorrhoea which could be corrected by thyroid feeding nor do thyroidectomized monkeys bleed after oestradiol has been given for 10 days and then stopped as do normal monkeys within a few days of oestradiol withdrawal

From the above experiments it is clear that thyroidectomy suppresses the pituitary luteinizing hormone and inhibits ovulation It may suppress the follicle stimulating hormone in the rat or may even stimulate its secretion in the rabbit but other experiments indicate that it does not influence F S H Thyroxin prevents the secretion of F S H and stimulates the secretion of L H

Another angle is the influence of sex hormones on the thyroid gland Castration in rats leads to some degree of thyroid involution the histology of the gland showing low cuboidal epithelium and colloid storage If thyroid hyperplasia is induced in rats by a goitrogenic diet neither ovariectomy nor oestradiol influences the degree of hyperplasia but induced thyroid hyperplasia (goitrogenic diet) in intact rats is ameliorated by progesterone Oestradiol is without effect in moderate doses but in very large doses necrosis hyalinization and fibrosis of the hyperplastic thyroid results All these important observations were made by Emge and Laqueur (1941)

Adrenals and sex function The adrenal glands have an important reciprocal relationship with the sex glands and in addition secrete androgens oestrogens and progesterone For a

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THYROID GLAND AND SEX FUNCTION

Apart from the fact that thyrotoxicosis is often associated with amenorrhoea or oligomenorrhoea and that thyroid extract has been given empirically for idiopathic menorrhagia for many years the clinician is often unaware of the important influence of the thyroid gland on sex function

Thyroidectomy in rats causes an increase in weight of the pituitary gland with an increase in number and vacuolization of the basophil and chromophobe cells and a decrease in the percentage of eosinophils If these pituitary glands are implanted or extracts of them injected into immature female mice the follicles and especially the corpora lutea are fewer and smaller than those of the control animals indicating diminished gonadotrophic potency of the pituitaries of thyroidectomized animals (Evans and Simpson 1930 Stein and Lisle 1942) The thyroidectomized guinea pig showed no obvious abnormalities of the

Selye McEwen and Collip (1936) were the first to show that in the rat mammary development is stimulated by testosterone Reece and Mixner (1939) obtained complete lobule alveolar development in spayed rats and Folley and others (1939) obtained good lobule alveolar development in monkeys Noble (1939) obtained duct and alveolar growth in the ovariectomized rat but not in the hypophysectomized rat There is therefore no doubt as to the positive influence of testosterone on breast development in an animal with an intact hypophysis Desoxy cortone may produce breast development in mice (Heuverswyn and others 1939) lobule alveolar growth in monkeys (Speert 1940) and gynaecomastia in man (Edwards and others 1938 Lawrence 1943)

Thyroidectomy does not appear to influence mammary development or may even stimulate it in adult animals although in immature animals it may prevent normal breast development (Nelson and Tobin 1937 Smithcors and Leonard 1942)

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Lactation

Stricker and Grueter (1928) first showed that an anterior pituitary extract could produce lactation in a pseudo pregnant rabbit The essential hormone was called prolactin and as it

full discussion the reader is referred to the chapter on the adrenal glands

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THE BREAST AND LACTATION

It is well known that the breasts usually develop at puberty when ovarian function becomes active Experimentally in the ovariectomized animal it has been repeatedly shown that oestradiol causes duct growth whereas progesterone develops the lobule alveolar system This is however not true for all species and in the ovariectomized monkey complete lobule alveolar development has been obtained by oestradiol without the addition of progesterone (Allen 1927) and similar results have been recorded in the ovariectomized cow (Walker and Stanley 1941) Similar results have been obtained with stilboestrol (Folley 1940) The breast of the normal or ovariectomized animal is less sensitive to oestradiol and progesterone than that of the female but with prolonged treatment similar results are obtainable

The conventional views on breast development were challenged by Gomez and Turner (1938 1942) when they found that oestradiol and progesterone were ineffective in the hypophysectomized animal By using pituitary extracts and the implantation of pituitary gland of animals treated by oestradiol or progesterone they postulated the existence of two pituitary protein like hormones Mammogen I and II which had actions on the breast comparable to those of oestradiol and progesterone respectively and whose production in the pituitary gland depended upon these ovarian hormones in fact that oestradiol and progesterone did not act directly on the breast tissue but via the pituitary gland These observations are not undisputed

Other hormones may play a part in normal mammary development and can certainly do so under experimental conditions

The use of prolactin for increasing the yield of milk in women has on the whole been disappointing although some have reported good results (Kenny and King 1939) Quite recently failure of lactation in women has been found to respond to Lugol s iodine (Robinson 1947)

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was found to stimulate the growth of the pigeon's crop gland this simple procedure was used for its assay Prolactin is found in the pituitary and sometimes in the urine of most species including man and in both sexes

The fact that a purified preparation of prolactin failed to initiate lactation in a hypophysectomized animal (Nelson and Gaunt 1936) led to the search for other hormone factors in lactation

Adrenals Adrenalectomized animals do not lactate but this function is restored by 17 hydroxy 11 dehydrocorticosterone and not by desoxycortone (Nelson Gaunt and Schweizer 1943) This suggests that a normal carbohydrate metabolism is essential for normal lactation especially as lactation in the depancreatized dog is also greatly impaired The prolactin content of the hypophysis of an adrenalectomized animal is normal

Thyroid Thyroidectomy may inhibit or decrease lactation but in some species no interference occurs (Petersen 1944) The administration of thyroid or thyroxine to intact lactating animals may increase the yield of milk and its fat content (Folley and White 1936) If however it is given in excess the lactation is decreased (de Fremery 1936) Several groups of workers (Barcroft 1945) have shown that iodinated protein fed to cows will increase the yield and fat percentage of their milk

Ovary Stilboestrol has been found to increase the prolactin content of the rat's pituitary (Lewis and Turner 1942) and also to stimulate secretion of the pituitary adrenotrophic hormone (Jones and Nelson 1942) Folley and others (1941) showed that stilboestrol could initiate copious lactation in the virgin goat It is also of interest that prolactin or a hormone closely associated with it (called luteotrophin) may cause the corpus luteum to secrete progesterone (Lyons Simpson and Evans 1941)

The cause of the absence of lactation during pregnancy and its initiation after parturition has been much discussed Inhibition of lactation during pregnancy by progesterone placental secretions distension of the uterus or by oestradiol have not been proved although injections of oestrogens and androgens inhibit lactation in some species if given within a short time of parturition Turner and Meites (1941) have shown that the prolactin content of the pituitary gland during pregnancy is low but it increases after parturition

CHAPTER XXXI

EUNUCHOIDISM AND EUNUCHISM

In the Male

Definition

A EUNUCH is a person who is castrated before puberty The term is usually limited to males A eunuchoid is a person who has the physical and psychological characteristics of a eunuch and whose gonads are and remain infantile In eunuchoidism the primary defect is in the gonads and not in the pituitary The term eunuchoid is usually applied to males Female eunuchoids exist but are less easy to diagnose clinically The present section will deal with males only

Aetiology

Males were castrated before puberty in Eastern countries for employment in the harem the Greek word eunuch meaning guardian of the couch Castration rendered them sterile and was supposed to abolish libido and potency Pre puberty castration has also been carried out for religious purposes in certain sects in Russia and Roumania e g les Skoptzy

The more definite causes of eunuchoidism are mumps and genital tuberculosis although the latter is rare before puberty A not uncommon complication of mumps is bilateral orchitis and atrophy of the testes may follow It seems probable to me that such atrophy may also follow mumps in the absence of clinical orchitis I think it is not unlikely that other virus specific fevers e g *measles* may attack the testes without clinical evidence Congenital syphilis typhoid and blackwater fever have been put forward as aetiological factors in eunuchoidism Operation for bilateral hernia is occasionally followed by atrophy of the testes if the blood supply is interfered with Trauma in accidents may be the case The commonest cause of eunuchoidism however appears to be genetic since the condition occurs in brothers and uncles and other members of the family may show evidence of incomplete eunuchoidism or long delayed puberty

B CLINICAL

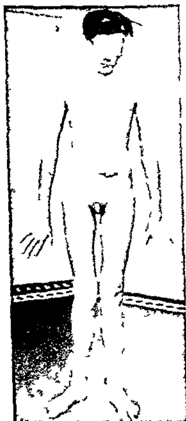
CHAPTER XXXIV

INTRODUCTION

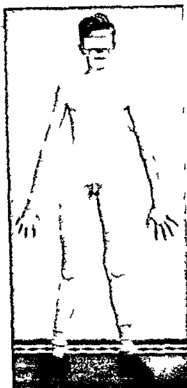
ENDOCRINOPATHIES affecting the gonads are the concern not only of the endocrinologist but also of the gynaecologist uro genital surgeon psychiatrist and sociologist It is the duty of the endocrinologist to investigate disturbance of gonadal function along the same fundamental lines as he would that of any other endocrine gland and to remember that the gonad is part of a closely interrelated endocrine system An obvious example of this is amenorrhoea due to an adrenal tumour At the same time the endocrinologist will recognize that a study of the gonads and accessory structures calls for a special technique acquired by those who devote their time to it and who have been systematically trained Again as an obvious example the endocrinologist should never be guilty of *treating uterine haemorrhage* by progesterone when the cause is cancer of the uterus It is also quite unjustified to regard the gynaecologist as a technician The gynaecologist is often a good physician as well and interested in his patient as a *complete individual* Further just as the cerebral surgeon e g Cushing has contributed greatly to our knowledge of endocrinology and especially of the pituitary gland so can and does the gynaecologist add to our knowledge of ovarian function He looks inside the abdomen while the endocrinologist theorizes Similarly biopsy of the testis by the urogenital surgeon has given us objective factual data in sterility

In considering clinical disorder of sex function we shall inevitably be overlapping with sections on the pituitary and the adrenals and some subjects might more appropriately have been dealt with in those chapters but the line of demarcation is arbitrary

October 1945 His previous history and development were similar to that of A N as were his general appearance and measurements (see photograph) He al o had mumps as a small child but no known orchitis



Case E 1



Case E 2

FIG 64 Two brothers aged 18 and ? illustrating familial eunuchoidism Failure of response to gonadotrophic hormone but immediate response to testosterone increasing weight and height and sexual maturity (Shown at Royal Society of Medicine Clinical Meeting March, 1946—*Proc Roy Soc Med* (1946) xxxix 511) (See text Case E 1 and E 2)

His measurements were span 69 in upper limb 30 in lower limb 40 in his height was 5 ft 6½ in and his weight 7 stones 8 lb He was still growing B P 105 60

Genitals his penis was infantile the right testis was pea like and in the scrotum the l ft testis was felt as a tiny tender spherical body above the left outer pubis it could not be brought down into the scrotum and appeared to be ectopic There was no axillary hair but a few pubic

Clinical

Since the many text book accounts of eunuchoidism are so variable and conflicting I have decided to present my own series of cases first and then draw up a clinical picture from them This is not possible in the case of eunuchism so that my evidence is drawn largely from Pittard s admirable book on the Skopecs The clinical features however are practically identical with those of eunuchoids

Eunuchoidism in Two Brothers

Case E 1 A Y age 18 a clerk was first seen by me on 14 September 1945 being sent up as undeveloped testes He had a brother aged 22 with a similar condition but his sister and father were normal his mother died of heart failure at the age of 33 but was otherwise normal

Past history measles scarlet fever and mumps when young child but no known orchitis The patient weighed 7 stones and was 5 ft 7 in in height He stated that he was still growing in height but not in breadth He had a boyish appearance and manner, and looked more like 12 years of age He was shy and diffident His intelligence was normal Measurements span 72½ in height 69 in breadth of pelvis 14 in Upper limb 30½ in lower limb 39 in breadth of shoulders 17½ in The fingers and toes were long and slender The patient was thin and the ribs showed through The penis was small as that of a boy of 8 The scrotum was small and the testicles only indefinitely palpable as minute bodies of fluid consistency There was no hair whatsoever on the pubis axillae body or face The voice was high pitched and unbroken Blood pressure 125/80 pulse 80 fundi normal X ray of pituitary fossa much smaller than average Delayed epiphyseal closure average for male of 15 years (Rohan Williams) 17 ketosteroids in the urine were 4 6 mg per day (3 2 mg per litre)

On 16 October 1945 I implanted eight tablets of 100 mg each of testosterone propionate in the subcutaneous tissue of the abdomen On 16 November 1945 the patient reported that during the past 3 weeks he had been having some six or more penile erections during the night and similarly during the day He had put on 1 stone in weight and his appetite was greatly increased His voice had become deeper He was much broader across the chest and much stronger on examination his penis was appreciably enlarged but his scrotum and contents unchanged A distinct redness or erythaema was present over the pubis penis and scrotum Some hair had grown on the pubis with upper horizontal delineation but no hair was present in the axillae or on the face On 4 January 1946 he had put on another stone in weight from 7 stones to 9 stones 3 lb altogether and further changes in the above direction were noted His manner was no longer shy and diffident

Case E 2 B Y age 22 came along to hospital because of his brother A Y s great improvement under treatment He was first seen on 26

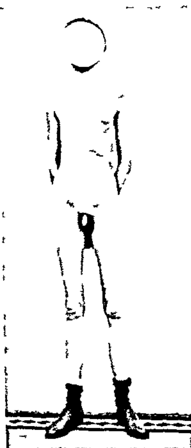


Fig 65 Eunuchoidism Male aged 23 height 6 ft 3 in tall thin type no proper puberty penis subnormal left testicle infant le and in scrotum right testis infantile felt above the right ectopic epiphyses ununited no response to gonadotrophins but good response to test te one (Pa t nt had a brothe b ft 1 in in he ght who was an incomplete eunuchoid) (See text Case E 3)

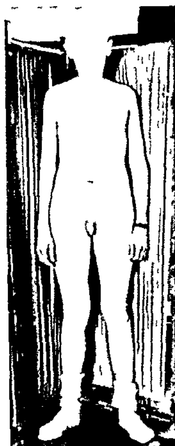


Fig 66 Eunuchoidism Aged 20 tall (5 ft 11 in) weight 133 lb moderately thin no hair on face or in axillae few pubic hairs appeared at the age of 18 voice not yet broken small penis and pea like testes no response to gonadotrophins but marked response to testo te one epiphyses ununited (See text Case E 4)

hairs which had been present for some years There was no facial hair In spite of this infantil sexual state he stated that he had erections once a week since the age of 13 and masturbated about once a week with resulting orgasm but no emissions His fundi were normal but he had myopia since the age of 5

In the previous 6 weeks he had received 500 units of gonadotrophic hormone of pregnancy urine (I C S H or interstitial cell stimulating hormone pregnyl) by intramuscular injection twice weekly making a total of 6 000 units There was no response except perhaps a few additional pubic hairs On 20 November 194 at his urgent request I implanted 6 100 mg of testosterone propionate subcutaneously with a similar result to that experienced by John

Case E 3 F G age 23 This patient complained of undescended testicles but he was strikingly tall and thin and looked much younger than his years (Fig 65) At 14 years of age he was 5 ft 9 in at 18 6 ft and at 23 he was 6 ft 3 in The weight was 9 stones He had measles and mumps in childhood but no obvious orchitis His voice had not broken and he had no sexual urge or potency

On examination he was seen to be tall and thin without facial or bodily hair and with a few scanty pubic and axillary hairs His fingers were long and thin His penis was small his right testicle minute and in the scrotum his left testis was also minute and ectopic being palpable above the external abdominal ring The span of his extended arms was 79 in The bone age was that of a lad of 15 Blood count normal carbohydrate tolerance 70 105 125 and 68 mg per 100 c c B P 130/86 The response to gonadotrophic therapy was negative and to testosterone therapy positive

It is of interest that this patient had a brother of 25 who was very similar in appearance but who had normal genitals and sexual potency He began to grow rapidly at the age of 16 and stopped at the age of 21 height 6 ft 1 in His puberty was delayed pubic hair first appearing at the age of 16 together with seminal emissions the voice breaking at age 18 and shaving starting at 21 To day he only shaves every other day and then it is not essential However his penis and testes are normal and his pubic hair of male type

Case E 4 K I age 20 This patient was brought along by his father because of his infantile genitals His voice had not broken he did not require to shave and he showed no interest in the opposite sex His school standard was normal He was of very placid temperament and a good stonewaller at cricket He was 5 ft 11 in in height and his father was 6 ft all the family being about that height

On examination he was seen to have a boyish appearance but his pelvis was distinctly wider than his shoulders His testes were small pea like bodies in the scrotum and his penis infantile A few pubic hairs were present and were said to have appeared at the age of 18 No other hair was present on the body or face B P 90/60 Pulse 66

The response to gonadotrophins was negative and to testosterone positive (Fig 66)

kissed his wife as a routine but without any feeling of affection or warmth

He had never played games at school he had never shaved his voice

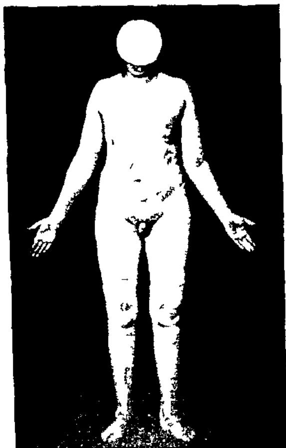


FIG 67 EUNUCHOIDISM Fat type male aged 36 at age 21 was 5 ft 10 in and 8 stone at age 26 was 6 ft 2 in and 12 stones at age 36 16 stones penis subnormal testes size of peas no response to gonadotrophins response to testosterone (See text Case E 6)

had never broken and he still sang in a high pitched boyish voice He was always of a quiet nature and would never argue or fight He believed that an uncle had been very similar to himself

He was 5 ft 8 in in height and weighed 10 stones 2 lb There were no fatty depositions His breasts were palpable and moderate gynaecomastia might be said to be present (A brother had similar breast

Case F 5 G I age 32 This patient illustrates the syndrome of eunuchoidism with normal or only slightly subnormal external genitals His presenting symptom was hot flushes followed by cold sweats occurring several times a day since the age of 13 He had never experienced any sexual urge or any erections and had never attempted intercourse or flirtation His voice had not broken and he had never shaved There *was some sensitivity to cold and general weakness There was no* history of mumps

His general configuration was not obviously abnormal although his facial skin was smooth pallid and hairless Height 5 ft 9 in weight 12 stones His scrotum and testes were of normal size and not infantile Pubic hair was small in amount and limited horizontally Axillary hair was very scanty and body hair absent The fundi were normal B P 120/80 Adequate treatment was never carried out but there was a partial response to 20 mg daily of methyl testosterone by mouth

Case F 6 B I K age 36 This patient originally came under observation because of undeveloped testes He stated that he had never masturbated or had nocturnal emissions but that he had normal sexual intercourse with ejaculation at the age of 18 He married at the age of 31 had coitus nightly for the first six months and then twice a month No children resulted He was tall and thin as a child and at the age of 21 he weighed 8 stones His height then was 5 ft 10 in In the next 5 years he grew to 6 ft 2 in and gained several stones in weight At the age of 36 he was the same height but weighed 16 stones

In spite of the normal coitus his penis was small (2 in in the flaccid *state) and the testes minute the size of small peas There was* little hair on the face and he shaved only once a month There was a little pubic hair with horizontal upper limit and a little axillary hair but the body was hairless Symmetrical fatty deposits were present on the chest and abdomen and chin and his appearance (Fig 67) is that usually described as characteristic of eunuchs although the fat is only moderate in amount B P 110/70 pulse 70

He failed to respond to gonadotrophic therapy but the response to testosterone was positive It is of interest that he has two brothers of similar build one 5 ft 10 in and weighing 15 stones the other 6 ft and 16 stones and both have children The brothers were not available for examination

When seen later at the age of 44 his condition was similar except *that prognathism with intervals between the teeth of* the lower jaw was more obvious The fingers were rather short and thick He claimed to be having a normal sexual life

Case E 7 P Z age 43 This patient married at the age of 29 although he had never experienced any interest in girls and had no knowledge of how children were produced The parents arranged the marriage He stated that he experienced some erections but they were usually too weak for coitus and he had never masturbated or had spontaneous *emissions* Occasionally he penetrated the vagina and indulged in rhythmic movements but deturgescence without emission followed in 2 minutes He

found in the scrotum The prostate is quite small and rarely palpable per rectum

Hair Pubic and axillary hair is nearly always scanty and the pubic hair does not ascend in triangular fashion to the umbilicus but is limited horizontally, as in the female There is little or no facial hair Some of the patients stated that they shaved once a month or once a fortnight The body and limbs are practically free from hair The hair over the head is luxuriant and baldness does not occur

Skin The skin of the face is soft in texture as in the female Although the haemoglobin and red cells are normal the face usually has a pallid appearance in contrast to the plethora that may be seen with Cushing s syndrome The face and body are usually free from acne although acne may make its appearance in the course of treatment with testosterone In one patient (E 7) acne had been present from the age of 14 but this must be regarded as very exceptional

Sexual behaviour Libido is usually absent Two patients married because their parents thought it the correct thing to do and the parents arranged the marriages In one of these two cases (E 8) he felt no affection for his wife and never attempted embracing or intercourse She left him In the other case (E 7) he stated that he kissed his wife as a routine but without any feeling of affection or warmth He had never masturbated or had nocturnal emissions but after marriage he experienced some erections which were usually too weak for coitus to take place Occasionally however he stated that he penetrated the vagina and indulged in rhythmic movements for some 2 minutes when deturgescence followed without emission or orgasm In only one patient (E 6) was there any claim to normal sexual intercourse He stated that this occurred with emission at the age of 18 He married at the age of 31 had coitus nightly for the first six months and then twice a month No children resulted Although experimentally the mating instinct seems to depend on the anterior pituitary gland rather than the testis adequate performance depends upon the latter and this patient must be regarded as exceptional if his story can be believed He added later that his wife had left him because his penis was too small but that he had found a woman lover and coitus was satisfactory Although eunuchs are believed

enlargement but no other endocrine features) Some pubic hair was present and slight axillary hair but no hair on the abdomen or chest and hardly any on the face A very unusual feature was the presence of scarred acne on the face which had been present for many years—he thought from the early teens The penis and scrotum were of moderate size but the testes were palpable as minute pea like bodies in the scrotum Epiphyses of the wrist and metacarpals were united B P 120/80 Pulse 60 Prolonged therapy with gonadotrophic hormone was without effect Response to testosterone was positive

Case E 8 J K age 31 This patient was originally treated by his doctor as a Frohlich s syndrome but he failed to respond to gonadotrophic hormone When 20 he had no pubic hair and very small penis and testicles During the past few years he had received intermittent treatment with testosterone and methyl testosterone in comparatively small doses I saw him first in August 1943 after some months of treatment The penis was bigger than it was before the above treatment but the testicles remained tiny His general configuration remained the same and although he was not really fat there were fatty depositions above the pubis and in the breast region abdomen and buttocks Weight 13 stones height 6 ft B P 120 60 He stated that he was very small at 14 very short at 16 and well below average height until 20 when he started to grow rapidly He believed that he ceased to grow at the age of 24 His parents had arranged a marriage some years ago but he had no libido or potency and his wife left him He was of docile temperament and good natured although he stated that he occasionally flared up When he came home from work he went to sleep in an arm chair until bed time He suffered from depression and headaches X ray of the skull was negative and the radial and carpal epiphyses were shown to be partially fused Response to testosterone in adequate dosage was positive

Summary of Clinical Features

Genital organs The testes are almost invariably minute pea like bodies such as might be found in an infant The penis is usually smaller than normal, and may be infantile in size The size of the penis is much more variable than that of the testes In one patient (E 5) the testes as well as the penis were apparently of normal size This is unusual but may be present when the clinical picture is otherwise quite characteristic of eunuchoidism It is probable in such cases that an inflammatory process has destroyed the interstitial cells without causing atrophy of the whole organ The scrotum is usually but not invariably smaller than normal In two eunuchoid brothers (E 1 and E 2) the left testis was ectopic in both The testes may both be undescended but more usually they are

gland to secrete growth hormone in normal or supernormal quantities The pituitary factor probably depends upon familial constitution Experimental castration leads to hyperplasia of the anterior pituitary gland so that increased secretion of growth hormone might well be anticipated in eunuchoids and castrates

The pelvis tends to be gynaecoid and is of greater breadth than the shoulders which is the reverse of normal males and similar to the skeletal proportion of females or intermediate between the male and female dimensions The discrepancy between shoulders and pelvis is more marked in some than in others

Gynaecomastia Breast development approximating to that of the female as distinct from localized fatty deposition occurred in only one patient in this series (E 7) It is interesting to note that he had a brother who also had a female type of breast but was otherwise normal

A syndrome characterized by gynaecomastia aspermatogenesis normal interstitial cells and increased secretion of follicle stimulating hormone has been described by Klinefelter Reifenstein and Albright (1942) The majority of these patients however showed clinical evidence of a variable degree of eunuchoidism e g span greater than supernormal height scanty facial hair and incomplete libido or potency This is perhaps surprising since testicular biopsy showed hyalinization of the seminiferous tubules but apparently normal interstitial cells Oestrogen secretion was normal and 17 ketosteroid secretion normal or subnormal Breast tissue showed ductal hyperplasia with proliferation of periductal connective tissue The authors could find no explanation of the gynaecomastia They point out however that one of their eunuchoid patients treated with testosterone developed gynaecomastia with a similar histological picture The primary lesion is believed to be a degenerative one of unknown aetiology starting in early life

Heller Nelson and Roth (1943) also describe gynaecomastia (not invariable) in a syndrome characterized by eunuchoid features atrophy or apparent absence of testes in scrotum inguinal canal or abdomen but the height was normal or subnormal in spite of delayed union of epiphyses Follicle stimulating and luteinizing hormones were excreted in excess End buds and alveoli were present in breast sections but no patients complained of pain and there was no evidence of mastitis

to be impotent, there is said to be a high incidence of gonorrhoea among them so that some sexual play is probable

In no patient in this series has there been any evidence of active or passive homosexuality although the latter might perhaps have been anticipated The series is too small for comprehensive conclusions on this point

Skeletal changes Nearly all these patients are tall in the region of 72 in, and the span of their outstretched hands is greater than their height Average height e g 68 in, may however be found e g case E 7 Among the tall eunuchoids they may have been above average height throughout life or the increased height was attained above the age of 18 when growth stops in normal people in eunuchoids growth may proceed until the age of 26 or later This is due to the delayed union of the epiphyses which is invariable The bone age in childhood or adolescence is younger than the chronological age The younger bone age and delayed union of the epiphyses are also found in infantilism and is almost certainly due to lack of androgenic secretion by the testes In contrast sexual precocity (q v) is associated with advanced bone age premature union of the epiphyses and an ultimate height less than average Some eunuchoids although eventually attaining a height above normal, may grow at a subnormal rate in childhood and adolescence This is probably due to the absence of testosterone secretion because in sexual precocity initial growth is more rapid than the average (see Physiology of Growth)

The fingers are usually long and thin but in one case E 6 they were rather short and stout Some patients are built on slender lines with rather thin bones but others are more sturdy In case E 6 acromegalic changes especially prognathism appear to have been superimposed in the third decade This is unusual but the primary diagnosis of eunuchoidism appears justified

Apart from the skeletal similarity of the two brothers E 1 and E 2 there are examples of other members of a family having similar build and skeletal structure but not being eunuchoid The patient E 6 had two brothers very similar to himself but both of them were married and had children Patient E 3 had a brother of 25 of 73 in in height

The height of a eunuchoid appears to depend both upon the delayed union of the epiphyses and the ability of the pituitary

eunuchoids are passive and accommodating They are not afraid but they have little pugnacity or external aggressiveness in their make up Their inertia may pass into somnolence Although it is rare for them to show skill in games one patient (E 3) was a very reliable stone waller at cricket In contrast to their general placidity they may exhibit phases of obstinacy contrariness sensitivity or irritability and may flare up like a prima donna Such outbursts or tantrums are usually short lived Eunuchoids are sometimes introspective and secretive and may be given to intrigue They may be depressed and have a sense of inferiority about their subnormal genital development Usually they are apathetic about women but if a marriage has been arranged (E 7 E 8) they deeply resent the scorn of their wives over their impotency

I have not seen genital homosexuality among eunuchoids but their gentle sympathetic nature coupled with an absence of interest in heterosexuality may lead them to positions of prominence in boy and male adolescent social activities

There is room for many departures from the above general picture and the writer knows of two eunuchoids (outside the present series) who have attained outstanding intellectual and social success

Family incidence Two brothers are described in this series (E 1 and E 2) but examples of three or four brothers and an uncle and other familial incidence have been described from time to time There is therefore no doubt that eunuchoids as other endocrinopathies may be familial as well as sporadic

One patient (E 7) who himself had gynaecomastia stated that a brother had this condition but was otherwise normal Another patient (E 6) said that two of his brothers were of identical build but were potent and fertile These examples of isolated features in other members of the same family although comparable to what is found with other endocrinopathies are not included in the term familial eunuchoidism but are worthy of note

The brother of patient E 3 whom I had an opportunity of examining is an interesting example of partial eunuchoidism apparently due to a belated and incomplete gonadal maturity Thus at the age of 25 he was very similar to his brother but had normal genitals and potency He began to grow rapidly at the

Adiposity or leanness Contrary to general belief eunuchoids are not fat or perhaps it would be more correct to state that many eunuchoids are not fat On the contrary there is often a conspicuous absence of fat and the e patients are lean In other eunuchoids although their general appearance is not that of a fat person there may be localized deposits of fat e g pubis breasts abdomen and buttocks Thin eunuchoids may become fat in middle age or earlier One patient (F 6) was tall and thin as a child at the age of 21 he was still very thin and weighed only 112 lb although his height was 70 in In the next 5 years he grew 4 in in height and put on 5 stones in weight and became adipose In this particular instance a phase of pituitary activity manifested by growth was also apparently associated with fat deposition

In our study of pre pubertal castration we shall see that leanness is at least as frequent as adiposity and probably more so The clinical and family studies coupled with the experimental evidence that in some species e g dogs 50 per cent only became fat after early castration (Korenchevsky) suggest that the reaction of the pituitary gland to castration determines adiposity or leanness and that the type of reaction is inherent *in the genetic endocrine constitution*

Cardiovascular system The blood pressure is normal or moderate hypotension may be found The pulse rate tends to be slow Radiography studies may show subnormal heart measurements which is not unexpected since testosterone given experimentally produces hypertrophy of cardiac muscle

Muscular system The muscles are poorly developed and flabby in most patients and eunuchoids are unable to do heavy muscular work or to play games requiring skill and stamina These facts may be ascribed to deficient secretion of androgens since the muscular development and increased strength normally associated with puberty fail to appear In contrast sexual precocity *is often associated with abnormal muscular strength*

Larynx The larynx tends to remain small and cartilaginous and the voice high pitched This may not be obvious except in emotional mood or on the telephone

Emotion and intellect Intelligence is normal and in some patients may be well above normal *The behaviour pattern* however shows many interesting features On the whole

The testes are nearly always minute but occasionally may be normal in size In the latter case one may suppose an initial normal development but a pre pubertal infection leading to degeneration (or hyalinization) of the interstitial cells and seminiferous tubules without however extensive fibrosis The penis is usually infantile but again in the latter group may be only slightly subnormal The prostate is rarely palpable There is an absence of bodily and facial hair although pubic and axillary hair may be present

We have seen from the case descriptions that the majority of eunuchoids are tall and slim Normal height does not exclude eunuchoidism Where the height is considerably below normal the diagnosis is more probably infantilism since there is an associated defect of pituitary secretion of growth hormone This aspect of diagnosis may prove difficult at an early age since some eunuchoids are below normal height until about 16 years of age or more even though their ultimate height is well above average This is because testosterone has also an important stimulating effect on skeletal growth and its absence or sub normal secretion may impair skeletal growth

Where a eunuchoid is fat the differential diagnosis from Frohlich s syndrome may prove difficult In Frohlich s syndrome the height is normal or subnormal There is however a group of cases where the diagnosis of Frohlich s syndrome might be justified at the age of 13 but who eventually develop full sexual maturity potency and fertility but retain feminine character istics e g horizontal limitation of pubic hair gynaecoid pelvis feminine walk and gestures This is a syndrome not hitherto recog nized systematically or classified but it is described in the pitu itary section of this book under the name adipose gynandrism

The fundamental differentiation of hypogonadism depends upon whether it is primary as in eunuchoidism or secondary to a pituitary deficiency as in infantilism and Frohlich s syndrome When accurate and easy methods of gonadotrophic assay of serum and urine are available a method of biochemical or biological differentiation will be possible gonadotrophins being normal or above normal in the former condition and deficient or absent in the latter (secondary) group A therapeutic test is treatment with gonadotrophic preparations since in eunuchoid ism there is no response whereas in infantilism as in Frohlich s

age of 16 and stopped at the age of 21 his height then being 73 in Pubic hair and nocturnal seminal emissions started at the age of 16 and the voice broke at 18 He began to shave at 21 but even to day at 25 he shaves only every other day and *says it is really not essential* His pubic hair was limited horizontally as in the female

Incomplete or partial eunuchoidism is probably more frequent than is generally recognized and may be present in both sexes It might well be described as a neutral sex having similar or identical physical and psychological characteristics and differing only in respect to external genitals

Apart from incomplete eunuchoidism in the male one not infrequently meets with a dissociation of androgenic effects Thus the genitals and libido are normal but the facial hair is almost non existent This is apparently due to an inherent *refractoriness to testosterone of the facial skin or an absence* of hair follicles since testosterone does not produce any striking effect Some of these patients may also have subnormal genitals (unresponsive to gonadotrophins) without however any of the skeletal characteristics of eunuchoids and clear classification is not always possible

I have no personal experience of males castrated before puberty but they are usually depicted as tall and fat The descriptions and pictures shown in Pittard s excellent book on les Skoptzy —a religious tribe in Russia among whom pre pubertal castration is undertaken—do not bear this out They are apparently tall and thin The only case of pre pubertal castration I have seen has been in a woman (see next section) and she is tall and thin Among eunuchoids there is a tendency to become fat in the forties or fifties the age of the *normal climacteric and this may be so among eunuchs* It is also probable that among races other than the Slavs pre pubertal castration is followed by adiposity although pictures of harem eunuchs in Pittard s book show them to be tall and lean

*In general I think it may be said that the physical and psycho*logical characteristics of pre pubertal castrates closely resemble those of eunuchoids

Diagnosis

Diagnosis is in accordance with the definition given above

and diffidence are lost Patients become extroverted creative energetic and sometimes aggressive They show initiative and are capable of assuming responsibility Depression and apathy disappear These changes are more marked in some than in others Hair grows more on the pubis and axilla and later on the body and face It is rare for the latter to grow at normal rate and this may be a question of inadequate dosage or inadequate responsiveness after a latent period or initial failure of development of hair follicles The voice becomes deeper

Disadvantages of treatment are the occurrence of acne in some patients which tends to disappear as the effect of implantation wears off and the occurrence of penile erections during the day as well as the night initially The advantages more than outweigh the disadvantages

If treatment ceases or wears off some residual physical benefits remain although libido and potency may disappear completely

In the Female

I have had an opportunity of observing one female eunuch castrated in infancy and a description of the case is given below The characteristics are I believe seen in some degree in many women patients with oligomenorrhoea but I am unable to give records as like most other clinicians I have not hitherto paid specific attention to eunuchoidism in females as an endocrine disorder The female being capable of playing a passive rôle in coitus although by no means always doing so eunuchoidism in females does not present itself so obviously as does eunuchoidism in the male Further there is no feature comparable to the absence of hair on the face or of a manly voice as in the male eunuchoid Although amenorrhoea or oligomenorrhoea is a feature of female eunuchoidism it is obvious that these disturbances of menstruation occur more frequently with other endocrine disturbances than with eunuchoidism

Case of a female castrated in infancy *J E* age 28 At the age of 6 months the patient had a strangulated hernia while in the heart of the country The local doctor removed a strangulated uterus with both Fallopian tubes and ovaries He was careful enough to demonstrate these to a local pathological society and the doctor who referred the patient to me (and prefers to remain anonymous) saw the specimen on the nature of which all were agreed

syndrome there is a positive gonadal response All these conditions however respond to testosterone therapy

The 17 ketosteroid excretion in eunuchoidism is usually in the lower levels of normality and sometimes subnormal Since however some patients show normal values it is not a method of absolute differentiation However the 17 ketosteroids measure both testicular and adrenal cortex androgens and the process in qualitative analysis will soon yield a method of differentiating these androgens so as to permit a further aid to diagnosis

Treatment

The specific treatment is testosterone propionate in effective dosage I have found the optimum treatment to be the subcutaneous insertion of 8 × 100 mg tablets (total 800 mg) of testosterone propionate under local anaesthesia I prefer the lower abdomen to the buttock or thigh as the site The technique is simple Local anaesthesia with 1 per cent novocaine 1 cm incision down to and through the subcutaneous fat which must be visualized the insertion of the tablets in the subcutaneous fat directly after use of sinus forceps or through a trocar and canula which must be kept dry, a single skin suture The effect commences in a few days and goes on for some 8 months when a repeat insertion is required Alternative treatment is 50 mg of testosterone propionate injected intramuscularly three times a week or 6 × 5 mg methyl testosterone *tablets by mouth or preferably dissolved under the tongue or* upper lip daily in divided doses

The effect of treatment is dramatic Libido and potency are restored and may be supernormal Orgasm occurs but detumescence may be delayed *Fluid emission is slight or* absent The wife obtains erotic satisfaction The penis and prostate grow in size but the testes remain infantile There is a remarkable increase in strength muscular development and weight The latter is largely due to muscular development since there is marked nitrogen retention There is also a remarkable increase in appetite which may have been previously normal or subnormal Fat eunuchoids may lose weight through diminished adiposity but thin ones gain some fat

Psychology and personality changes are remarkable Shyness

their height is always subnormal Their failure to grow is explained as a coincidental deficiency of pituitary growth hormone secretion or of pituitary adrenocorticotrophic secretion The syndrome has some comparable features to that described by Heller Nelson and Roth in men (see above)

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At the age of 28 when I saw the patient she was a beautiful tall slim woman with all the feminine graces and instincts and exceptionally intelligent Her height was 68 in and her span 69¼ in As in the cases of some of my male eunuchoid patients her height was normal or slightly subnormal in her early teens Thus by the age of 18 she was only 62 in but in the next year or so she grew 6 in and then stopped Her family were not tall Her shoulders were broader than her pelvis which was of the long narrow type The bones of her chest were rather prominent Her fingers were elongated and elegant The weight at the age of 24 was 105 lb The breasts were conspicuous by their absence and the nipples were minute There was a general absence of fat and the chest was flat like a thin male The face was slightly on the thin side but not especially so and was well shaped and comely The skin and complexion were good There was a slight amount of hair on the upper lip and sides of the face which was supposed to have been present from childhood There was no hair on the body and the genital hair was more vulval than pubic although some pubic hair was present Hair was also present under the arms The vulva were normal the vagina smaller than normal with a narrow entrance and the uterus and ovaries were found to be absent on examination under anaesthesia although at a later date a similar examination indicated a vestigial uterus or remnant of uterus about the length and width of the terminal phalanx of a little finger The blood pressure was 120/80 and the pulse 68 The urinary 17 ketosteroids were 11 2 mg in 24 hours (normal 5 to 12 mg) which suggests that the adrenal cortex was functioning normally or possibly above normal activity X ray of the bones of the wrist showed adult development and union of the epiphyses although the line of union of the radial epiphyses was still clearly visible

Treatment was with stilboestrol 10 mg daily and later with dienoestrol 1 mg daily There resulted a considerable development of the breast tissue and of the nipples which developed a pigmented areola a broadening of the pelvis an increase of some 10 lb in weight with probable diffuse fat deposition of slight degree an amazing improvement in general well being and psychological attitude to life In particular the patient was very pleased with her breast development and felt an adequate woman in all respects except the absence of fertility which she deplored

The characteristics of eunuchoidism in the female are comparable to those described in the female pre puberty castrate (see above) and to those of male eunuchoidism

As an anomaly but nevertheless factual one must record the syndrome of Albright Smith and Fraser (1942) of primary ovarian insufficiency with decreased stature Although these patients have eunuchoid proportions and characteristics and delayed bone age and the follicle stimulating hormone excretion is above normal they cannot be described as eunuchoid since

In 1916 wh n 27 his testicles had been shot away during battl Since that time his penis had become apparently smaller and libido and potency had disappeared although previously both were normal If

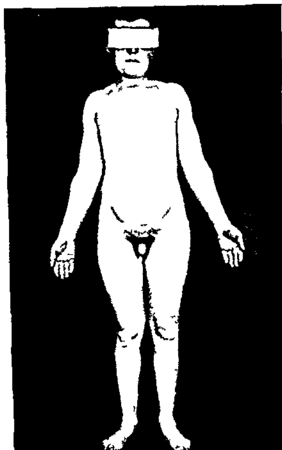


Fig 68 Mal aged 45 post puberty war castrate testicle shot away in 1916 after wh ch shaved rarely lost appet te and weight claims to have had coitus and orgasm without emission (See text Case S 3)

his bladder were full he sometimes experienced partial penile erection He was generally depressed but he stated not about the impotency While previously shaving daily he now did so twice a week and it is questionable whether this was really necessary The patient believed that the hair of his head and eyebrows had become a lighter brown During the pa t 3 years he had experienced hot an l cold sweats His

CHAPTER XXXVI

POST PUBERTY CASTRATION

IN this section also because of the varied accounts in text books often based on other text books or literature I prefer to draw a clinical picture based on my own experience I shall therefore describe the cases before writing the clinical picture and it will be convenient to treat males and females separately The lack of uniformity of response to castration after puberty and in some cases a glaring contrast or anomaly are striking At the same time other features follow as a sequel with some consistency

In the Male

Case S 1 K L age 21 This patient was said to have had a normal puberty at the age of 13 and during adolescence had experienced some masturbation and nocturnal seminal emissions In April 1945 at the age of 21 he was wounded in battle in the left groin and both testicles had to be removed surgically He commenced intermittent treatment with methyl testosterone by mouth in December 1945 but before this between April and December he experienced nocturnal dreams with slight fluid emissions and he masturbated once weekly with resulting erection and emission Frequent hot flushes followed by cold perspiration started in September 1945 and were partly controlled by 30 mg methyl testosterone by mouth daily and completely by double this dosage His voice broke at the age of 14 and had not changed following the accident He stated that he did not require to shave until he was 18 years old and the accident had no effect on his daily shaving He had a rather scanty moustache and did not appear to have a hairy face that would require daily shaving His height was 6 ft 0½ in and growth had ceased at the age of 18 His span was equal to his height His weight was 13 stones and he had put on 1 stone since the accident He attributed the increased weight to lack of exercise through a stiff knee and his surgical wound

On examination he was seen to be a tall slim type with narrow shoulders and only slightly wider pelvis The fingers however were not long and slender but rather average His penis was quite large No testicular tissue could be felt in the scrotum The pubic hair was normal in amount and of male type ascending along the linea alba Axillary hair was moderate He also had some hair on the chest B P 120/80 Pulse 60 (This patient appears to have been incompletely eunuchoid before the surgical castration)

Case S 2 A C age 49 This patient was seen in 1938 at the age of 49

tion for the treatment Under the influence of testosterone propionate the beard grew more rapidly and the patient shaved every day He was under the impression that the hair of the head was falling out Acne and pustules appeared to be an annoying complication of treatment diminishing when injections ceased

Subcutaneous insertion of testosterone propionate tablets In May June and July no treatment was given the patient relapsing into his former condition and the weight falling to 147 lb On 24 August I inserted four tablets 50 mg each of testosterone propionate subcutaneously in the lower abdominal region After local infiltration with novocaine a small incision down to and through the subcutaneous fat was made sinus forceps inserted upwards in the fat to make a small pocket and the tablets pushed in the wound was closed with a silk suture and healed perfectly The effects began 3 days after the insertion of the tablets and were similar to those observed with the injections but the effect was of greater intensity and more persistent A week after insertion of the tablets successful coitus was achieved several times nightly The patient did not feel any exhaustion or sense of fatigue following repeated coitus and was of the opinion that he could function polygamously without any limitation to his capacity Erections occurred several times during both day and night The patient appeared to be in a state of sexual euphoria and said that his wife could not keep pace with him With the injections of testosterone propionate detumescence had occurred following coitus but since insertion of the tablets detumescence did not occur for some 30 minutes after coitus which latter nevertheless was followed by a sense of relief and satisfaction After one month the weight increased to 148 lb The pulse rate was 70 and the blood pressure 155/85 Acne was not troublesome There was no evidence of gross prostatic enlargement The migraine on the whole was not troublesome but headaches of lesser severity occurred on 10 September 18 October and 19 November

Seen on 19 October the patient reported diminished sexual activity and desire coitus taking place every other night the weight was then 151 lb on 23 November the patient stated that there had been a distinct waning of sexual potency during the past few weeks coitus only occurring once a week being followed by tumescence and slight tiredness He still shaves daily but no hair on linea alba The weight was still 151 lb Photographs before and after treatment show increased muscular development increased fat deposition increase in size of penis and thickness of pubic hair Appetite was much better and he could now tolerate fatty foods which he could not prior to testosterone therapy Psychologically there has been a change Previously the patient was listless and apathetic with no energy and no initiative felt like someone dying since treatment he is more exhilarated interested in his surroundings and activities He feels as if he wants to go out and about and is looking for work

Comment Similar effect of testosterone propionate in a male castrate had been shown by Foss Kenyon and others but I could find no record

daughters aged 22 and 16. Since castration sexual desire had completely disappeared, the penis had become smaller, and only an occasional transient erection occurred, usually in association with a full bladder. He did, however, attempt coitus about once in six months, and although unsuccessful he did obtain some sort of an orgasm without emission which left him weak and depressed. Hot flushes alternating with cold sweats began a few months after castration and persisted for some 3 years, after which they gradually disappeared. Severe migrainous headaches also occurred shortly after operation, and had become more severe recently, lasting 2 or 3 days, appearing at intervals of a fortnight and associated with vomiting. He had had bilious attacks from childhood. He had lost over a stone in weight since castration and now weighed 142 lb.

On examination one was impressed by the pallor of his face, reminiscent of patients with a parapituitary cyst or chromophobe adenoma of the hypophysis. This pallor was also present in other male and female castrates that I had examined, and was in contrast to the plethora that occurs in Cushing's basophil syndrome, perhaps surprisingly so if castration produces an increase and degranulization of the basophil cells. The skin was also smooth and almost hair free. Pubic hair was thin and limited horizontally as in the female (the patient believing this had always been so); the axillary hair was scanty; shaving was hardly necessary once a week.

In contrast with the popular conception that castration leads to adiposity, the patient was lean and had lost weight since castration. This was complicated by the theoretical possibility of tuberculosis elsewhere, but it is equally true of others castrated in adult life. Prepubertal castration probably leads to adiposity. Even in post pubertal castrates there was some tendency for localized deposition of fat, e.g. suprapubic and cervical. The pulse rate was 60 per minute and the blood pressure 140/80. On 6, 7 and 8 December he received 25 mg. of testosterone propionate daily. On 7 December he experienced four penile erections in 24 hours. From 9 December onwards the dose was increased to 50 mg. daily. Erections occurred several times a day, lasted as long as 15 minutes, and were associated with a tingling at the base of the penis. He desired to have coitus and wished to go home to his wife. His weight increased from 142 lb. to 151 lb. in 3 weeks, and his general demeanour was more cheerful and alert. In the latter part of January and the first half of February injections of testosterone propionate were continued, 50 mg. three times weekly, and the patient reported successful coitus with his wife once or twice a week. He believed there was a slight amount of sticky fluid emitted. *On the cessation of injections libido and potency were soon lost, but regained again on recommencing for a few weeks in April.* The migrainous headaches disappeared after a month of treatment and returned when treatment was interrupted. Weight also tended to fall when treatment ceased.

On 29 April 1938 the patient wrote in terms of warmest apprecia-

female He was discharged from every job because he failed to get on with people was very sensitive had many rows and was lazy He cried easily and did so many times during the initial consultation without obvious immediate cause Nevertheless he was possessed of considerable charm of manner and in many respects was a very likeable personality As with the others there was no evidence of intellectual disability in itself but lack of application active interest and consistency might be mistaken for an intellectual defect

Libido and sexual function Libido was usually deficient or absent but it was difficult to decide how much this was determined by absence or lack of potency The penis almost invariably became smaller and this was accentuated by its flaccidity The prostate was involuted

With the exception of one patient (S 3) sexual intercourse did not occur and was really not possible before treatment In this patient (S 3) surgical castration occurred at 23 he married at 28 and during the honeymoon had sexual intercourse daily with orgasm and satisfaction to himself and his wife but without fluid emission Such intercourse continued for years but not quite so frequently There is no doubt from the history and clinical picture that he was a complete castrate but in spite of that we must accept a convincingly told history of satisfactory sexual intercourse In another patient (S 1) erections masturbation and seminal emissions occurred in the first few months after castration before treatment was commenced This continued after treatment as well as might be expected In the other three patients there was a complete or almost complete absence of erections and of coitus which was not found possible In two of these patients S 4 and S 5 however transient erections might occur occasionally when the bladder was full and in the latter patient he attempted coitus and succeeded in some measure about twice a year the act being followed by weakness and depression

Hair In all cases there was an absence of general bodily hair and the hair on the legs and arms was absent or minimal Most patients forgot whether this was so before castration or not Pubic and axillary hair were rather less than normal and the pubic hair was always limited horizontally in its upper border as in the female In one patient (S 4) the pubic hair

of a male castrato treated by testosterone propionate tablets inserted subcutaneously. The method is based on the experimental work of Parkes and Deanesly, who showed that tablet implantation led to a prolonged action. *In this case the effect is waning in the third month* but still persists. I have had beneficial results in a menopausal woman whose symptoms were hardly controlled by 50,000 units of oestrin injected twice weekly but readily abolished by the insertion of 60 mg oestrone subcutaneously. The method is capable of application in other endocrine fields. (Above comments: Simpson, 1938.)

Clinical Picture

General. On the whole the patients are not fat, although local fatty depositions, e.g. on pubis, breasts, abdomen, resulted in some patients. This was most marked in the patient castrated soon after puberty, namely at the age of 16 (S 4). None of the others could be described as adipose (see photographs). Two patients lost weight and appetite after castration, which is not unexpected in view of the increased appetite and increase of weight that follows testosterone therapy.

In all cases the face had a pallid appearance that was not due to anaemia, but which is also found with destructive lesions of the anterior pituitary gland, e.g. chromophobe adenoma or craniopharyngioma, which are followed by hypogonadism and other secondary deficiencies. In contrast to the pallor, dark circles may be present around the eyes. In addition to the pallor, and apart from absence of hairiness, the skin was soft and smooth and of delicate texture, as is usually found in the female. The muscles were flabby and strength subnormal. One patient (S 4) had been a very good all round athlete before the castration but not at all athletic subsequently. He was the only one who developed a gynaecoid pelvis, and this may be ascribed to the early age of castration, namely 16.

The voice usually remained unchanged. In one patient (S 3), however, he stated that a good singing voice had been lost after castration and replaced by a gruff croaking voice, which was not high pitched. In another patient (S 4), castrated at 16, the voice was high pitched.

Psychological. Most of the patients were placid in temperament and lacked initiative, drive and aggressiveness. One of them (S 3) slept 14 hours a day. In the patient castrated at 16 (S 4) the character was that of an artistic, temperamental

usually followed by regeneration and further cyst formation The condition may or may not be associated with menorrhagia Removal of both ovaries may be the only method of dealing with such a condition in view of the attacks of pain Where menorrhagia exists without pain bilateral ovariectomy should not be undertaken in women under 40 as the endocrine results may be serious Hysterectomy is a much more suitable procedure without resulting endocrine disturbance Radium or deep X rays destroy the ovaries and physiologically speaking these procedures are no different from surgical castration in their effect They too therefore should not be used in women under 40 The cause of menorrhagia is discussed under that heading

The following cases illustrate the above observations and show the variability of the clinical picture following removal or destruction of the ovaries

Complete Ovariectomy

Case O 1 Mrs L I age 40 This patient was referred to me by Mr A Bourne She was born in 1904 Menstruation commenced at 12 and occurred at intervals of 10 days lasted 7 days and was always slightly profuse Nevertheless in 1931 she conceived and had a live baby In August 1932 violent pain in the right iliac fossa led to a laparotomy and Mr Bourne found free blood in the peritoneum and a ruptured Graafian follicle He removed a cystic right ovary In December 1933 a similar attack was found to be due to a ruptured cyst in the left ovary The cystic part of this ovary was removed There then followed depression irritability backache and abdominal pain She developed many hysterical features including bleeding from all finger nails the result of artefacts From 1933 to 1936 she had scanty menstruation at intervals of a few months In May 1936 Bourne removed the remains of the left ovary because of abdominal pain and she was then a complete castrate at the age of 32 From that time on she had complete amenorrhoea

No hot flushes or other disturbances followed the complete ovariectomy nor did she gain in weight Her photograph (Fig 70) in 1944 shows a well proportioned woman perhaps rather thin and with moderately well developed breast She stated that her general condition had improved enormously As she had intermittent oestrogen therapy the only definite conclusion I would draw is that castration had not resulted in adiposity Her blood pressure remained normal 124/82

Bilateral Ovariectomy

Case O 2 Miss R C age 42 Unmarried The patient was referred to me by Mr Christie Brown In 1935 he excised a cyst from the right

had been shaved before his operation and it had only returned in scanty fashion leaving big areas with little or no pubic hair

The hair on the sides of the face and the chin was minimal or absent This was probably not quite so true of the hair on the upper lip and one patient (S 4) had a slender moustache But here too its thickness and growth was certainly subnormal Some of the patients stated that they shaved once or twice a month but as far as could be ascertained, this was not really necessary and the growth of hair on the face never attained the degree or character of that found in normal men One patient thought that the hair of the head and eyebrows had become a lighter brown There was no evidence of actual or incipient baldness in any patient

Hot flushes Hot flushes and cold sweats comparable to those met with in climacteric women did not appear immediately but a few months after operation They were not referred to by some patients and cannot be regarded as an invariable sequel In one patient (S 5) they disappeared after 3 years In another (S 2) castrated at 27 the hot flushes did not appear until the age of 41 All these variabilities are also met with in ovariectomized and climacteric women

In one patient (S 5) severe migraine started after castration and continued for many years

Treatment

This was by testosterone as described under Eunuchoidism The response was equally dramatic There was a return of libido and potency increased appetite and in some patients a gain in weight increased muscular strength a more virile outlook on life with greater initiative and drive and an amazing improvement in general well being and psychological outlook

In the Female

Castration is performed in adult women for two main causes (1) ovarian cystic ovaries associated with attacks of pelvic pain and (2) intractable menorrhagia which fails to respond to hormone therapy or curettage The pain in the first group may be due to haemorrhage into a cyst with resulting distension or rupture of the cyst or other cause and first one ovary and then another is removed Removal of a portion of an ovary is

a cystic left ovary was removed and she was then a complete castrate Amenorrhoea and hot flushes followed and the latter were controlled by oestradiol The photograph taken in 1943 (Fig 71) shows

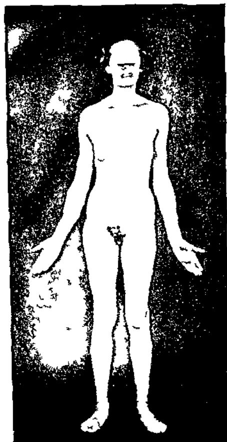


Fig 71 Complete post puberty castrate aged 43 removal in two stages of bilateral cysti ovar es owing to pain and intermittent menorrhagia followed by complete amenorrhoea but no adiposity (See text Case O -)

that no increase in weight resulted Her general subjective health was greatly improved but she continued to have anxiety symptoms which had been present for some 10 or more years Her breasts are seen to be mod rately develop d but this may be the result of oestrogen therapy Her blood pressure remained normal 1_0/80

ovary and carried out appendicectomy Menstruation had always been profuse lasting 8 days but with 4 week intervals She was tall and thin but had a marvellous appetite All her relatives were tall and

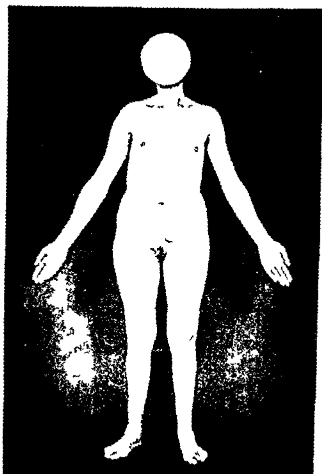


FIG 70 OVARIECTOMY CASTRATE Complete post puberty castrate without adiposity aged 40 at age of 30 right ruptured cystic ovary removed and a year later left ruptured cystic ovary removed after which amenorrhoea (See text Case O 1)

thin Owing to intermittent pelvic pain the remains of a cystic right ovary were removed by Mr Christie Brown in 1938 Menstruation became less profuse lasting 5 days and occurring at intervals of 3 or 4 weeks In 1939 menstruation again became profuse lasting 8 days and occurring at intervals of 4 to 5 weeks She also experienced attacks of sharp pains in the left iliac fossa These continued and in 1941

gone bilateral ovariectomy The results do not depend on the method used

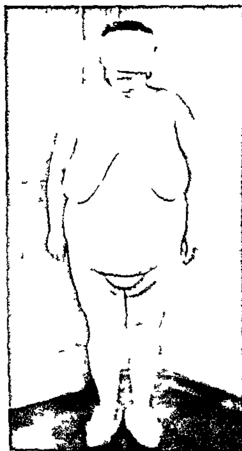


FIG 7 OVARIECTOMY ADIPOSITY Complete radium castrate aged 43 menorrhagia since puberty unresponsive to repeated curettage at age 24 castration by radium since when amenorrhoea and increasing adiposity before radium 9 stones 6 months later 1 stones 3 years later 18 stones now 20 stones (See text Case O 4)

Adiposity Contrary to general belief three of the four patients did not become obese and two of them (O 1 and O 2) remained thin One patient (O 4) however became fat in a dramatic and pathetic fashion gaining 3 stones in the 6 months

Radium Castrate

Case O 3 T M age 32 At the age of 21 this patient was treated with radium for menorrhagia and has since not menstruated During the next 12 months after radium she became very pale and her weight increased from 8 to 10 stones Her face became coarse and puffy Also during this year but not subsequently she experienced hot flushes choking sensation and palpitations There were serious psychological changes Whereas previously she had enjoyed going about e g dancing and sports *she was now very self conscious and depressed crying easily* She was a nursery governess but was unable to keep her jobs She felt she was different from other people

At the age of 32 her weight was 9 st 7 lb and there was no real indication of obesity Her breasts were of quite considerable size unless one assumes it is all fatty deposition Her pubic hair was perhaps subnormal in amount and the axillary hair was slight Her face was *hairless and pale* The body was hairless *Blood pressure 116/74* Her condition was not influenced by oestrogens

Radium Castrate

Case O 4 Mrs S I age 43 Menstruation commenced at the age of 10 occurred every [illegible] weeks and lasted 7 days From the age of 20 to 23 menorrhagia was almost continuous At the age of 23 she was delivered of a still born baby and stated that irregular menstrual bleeding continued during the pregnancy and subsequently Repeated curettage failed to stop the bleeding and at the age of 24 she had a castration dose of *radium since when amenorrhoea has persisted Her weight* before the radium was 9 stones 6 months later it was 12 stones and 3 years later 18 stones to day 20 stones (280 lb) Her height was 5 ft 3 in and had been so since the age of 9 She stated that her appetite was not big

Hot flushes were not experienced immediately after the operation but had been present for the last 2 years and were worse during the past 6 months She was a *professional singer with a mezzo soprano* voice unaffected by ovariectomy Her sexual life was said to be normal Her husband was a baker and she worked hard apart from her singing in the bakehouse She claimed that she perspired all day long like a wet rag but never lost weight

Her fatty depositions are seen in Fig 72 and a localized suprapubic pad of fat is noticeable Fundi normal blood pressure 110/70 pulse 68 *white linea distensae abdomen Her condition was not influenced* by oestrogens

Results of Castration in Adult Women

Although *castrare* means to cut the word castration can be applied to women whose ovaries have been destroyed by radium *or deep* X rays as well as to those who have under

Amenorrhoea Amenorrhoea follows invariably if the removal or destruction of the ovaries is complete

Cardiovascular system There is no evidence of hypertension following castration in the author s cases

Psychological disturbances These are variable One patient (O 1) was considerably better and a severe pre existing hysterical neurosis disappeared Another (O 2) experienced some amelioration in a pre existing neurosis A third (O 3) was seriously disturbed by radium castration whereas she had previously enjoyed a normal life enjoying herself with dancing and athletics she now felt different from other people and was reluctant to go about She was self conscious depressed and given to crying very easily In the fourth patient there were no gross psychological disturbances in spite of the enormous adiposity She had the good nature often associated with fat people

Other features Pubic and axillary hair remained although it might be less in amount There was perhaps a tendency for the hair of the head to retract in the temporo frontal region No change in speaking voice was noted and one professional singer with a mezzo soprano voice stated that castration had not impaired her voice This is in contrast to the experience of a male castrate in whom the singing voice became gruff and croaking The face tended to become pallid in the male castrates

Treatment

The obvious treatment is with oestradiol or the synthetic stilbóestrol group (for details see Climacteric section) It seems desirable to initiate treatment without delay and to use as large a dose as is compatible with the avoidance of excessive uterine haemorrhage until it becomes clear that the patient is not likely to develop obesity The latter when established is uninfluenced by oestrogen therapy

The treatment of castration obesity is that of obesity in general (see that section) and the condition is a refractory one

The fundamental treatment of castration in women is paradoxically speaking the avoidance of castration wherever possible In my opinion it should never be undertaken for menorrhagia in women under 40 the operation of choice being hysterectomy Clinicians and patients are sometimes tempted

following radium castration and within 3 years her weight was 18 stones compared with an initial weight of 9 stones Her final weight was 20 stones (280 lb) The increase of weight was so rapid that it must be regarded as a direct result of castration *Whether or not a patient will become obese after castration* probably depends upon the character of the response of the pituitary gland and thus is inherent in the endocrine constitution of the individual Another factor of a different kind appears to be the pre existence *of an anxiety neurosis If the patient is* of the worrying type who in spite of an excellent appetite fails to put on weight there appears to be less chance of her doing so after castration than there would be in a normal or sluggish type

Oestrogens do not influence castration adiposity Whether their administration immediately after operation and continuously *would prevent the pituitary changes leading to adiposity* is uncertain but theoretically possible One practical difficulty is the administration of adequate doses of oestrogens when the uterus remains intact as uterine bleeding is often a troublesome feature with high dosage

Hot flushes One patient stated that she had not experienced hot flushes after castration Another was greatly troubled by hot flushes choking sensations and palpitations for one year after radium castration at the age of 21 but not subsequently In one patient hot flushes started soon after castration and persisted In the obese castrate hot flushes did not occur after *the radium castration at the age of 24 but commenced at the* age of 41 This would indicate as in one male castrate that the mechanism responsible for vasomotor disturbance is not entirely *dependent upon the immediate results of gonadal destruction or* removal but upon other changes that occur in middle age at the period of the climacteric These are probably of pituitary origin since hot flushes and cold sweats following ovarian destruction or at the climacteric are associated with an excessive secretion of pituitary gonadotrophins Effective oestrogen therapy is followed by disappearance of the vaso motor symptoms *and of the excess of gonadotrophins*

Sexual life There is no evidence that castration in adult women affects libido or capacity for satisfactory coitus or eroticism

CHAPTER XXXVII

THE CLIMACTERIC

Definition

By climacteric or critical period or change of life is meant that readjustment of endocrine balance over a period of several years of which the menopause (cessation of menstruation) is an abrupt and conspicuous manifestation The menopause is not necessarily the initial manifestation of the climacteric and frequently endocrine changes begin to take place before menstruation ceases Though cessation of ovulation usually coincides with the cessation of menstruation an unexpected pregnancy may still occur

The conception of the climacteric as a physiological castration is a working hypothesis (not completely adequate) which permits a rational conception of endocrine changes but it does not explain the period of excessive oestrone formation preceding the ultimate ovarian failure nor does it explain how an artificial menopause at say 30 may be followed by a recurrence or exacerbation of menopausal symptoms at 45 Nevertheless failure of ovarian function seems to be the primary endocrine disorder since the pituitary becomes over active rather than under active and climacteric symptoms do not follow an ovarian failure that is secondary to pituitary failure as in craniopharyngioma further the endocrine changes following experimental surgical or radiation castration resemble in some respects those of the climacteric

Physiological castration In animals castration results in enlargement and hyperactivity of the pituitary gland (anterior lobe) and of the adrenal cortex with an increase in intra abdominal (and other) fat Castration cells of basophil nature appear in the pituitary and the number of basophil cells also increases by varying the species of animal and the physiological state at the time of operation all the trophic influences of the pituitary on other endocrine organs can be shown to be increased Thus in the guinea pig increase in thyrotrophic hormone occurs with resulting thyroid hyperplasia and adrenal

by the comparative ease and bloodlessness of radium or deep X rays to adopt these latter procedures but the potential ill effects are just the same as with bilateral ovariectomy Where cystic ovaries are associated with recurrent painful attacks bilateral ovariectomy might be inevitable A small portion of ovary should be left if possible although there is admittedly a considerable danger of its extensive regeneration with cystic formation The possibility of grafting a foetal ovary or a piece of adult ovary should be considered The giving of oestrogens cannot be considered to be complete replacement therapy apart from the difficulties indicated above Whether the addition of progesterone would render this substitution therapy complete is not certain but cost is an adverse factor However some patients sustain the operation with little or no discomfort The difficulty is to anticipate the response in each individual

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cortical hyperplasia in the rat may result from an excess of pituitary adrenotrophic hormone

Much of the symptomatology of the climacteric can be explained in this way but the kind and degree of change still depend on the underlying endocrine constitution Where this is well balanced the changes may be minimal but in so called endocrine types (e g tendency to adiposity at puberty and in pregnancy) gross changes take place *This is also true of animals* and only some 50 per cent of dogs grow fat after castration

That removal of an organ e g ovaries should produce an increase in its corresponding pituitary trophic hormone seems pointless from a teleological view since there is no object in increasing the amount of gonadotrophic hormone if there are no gonads to be stimulated However the mechanism may be of use in some circumstances e g when a small piece of ovary is left after a gynaecological operation But it may otherwise be harmful e g when a surgical remnant of thyroid under influence of thyrotrophic hormone undergoes hyperplasia and produces a hyperthyroid recurrence

Approximation to Cushing s Basophilism Syndrome

As an increase in pituitary basophil cells (with degranulation) and hyperplasia of the adrenal cortex are major results of castration in certain animals some resemblance of the climacteric syndrome to Cushing s syndrome is not surprising Adiposity virilism hypertension and impaired carbohydrate tolerance may be features of both conditions and in addition plethora and a tendency to bruise or bleed are not unusual

Adiposity The adiposity of the climacteric affects the face neck trunk, and upper arms but the extremities are often slender Symmetrical lipomas may be present and when painful and associated with a miserable outlook the condition is sometimes labelled Dercum s adiposis dolorosa Excessive hunger amounting to gluttony may be a feature and the possibility of hyperinsulinism from an excess of pituitary pancreatotrophic hormone might be postulated The adiposity may be refractory to dieting and extracts of thyroid unhelpful (Adiposity is probably due to hyperfunction of the pituitary rather than to hypofunction as commonly conceived)

Virilism Nearly every male characteristic is represented in

slight degree in the female and at the climacteric the down on the upper lip and chin become thicker Sometimes the hair is sufficiently coarse and luxuriant to form a moustache and beard causing mental anguish Hair may also increase at the sides of the face and the pubic hair extend along the linea alba up to the umbilicus Hirsutism however rarely assumes the proportions and extensive distribution of pathological virilism In one young woman with a pre existing tendency to virilism double ovariectomy for a gynaecological condition produced severe hirsutism The pubic hair tends to become uncurled at the climacteric Loss of scalp hair coincides with the development of facial hirsutism The voice becomes deeper and more powerful and singers find themselves able to reach notes lower than any previously possible the upper notes sometimes becoming more difficult of attainment

A change in mental outlook with an approximation to male characteristics also takes place greater resolution command initiative originality and administrative capacity being shown with the attainment of considerable commercial or parliamentary success in later life These changes really develop a year or more after the menopause and are perhaps more correctly termed post climacteric The physical manifestations of virilism are largely due to the hyperplasia of the adrenal cortex probably brought about by a pituitary corticotrophic stimulus It is of interest that patients with Addison s disease (personal observations) may show considerable amelioration or cure at the climacteric, although there is an initial phase in which the disease appears to be aggravated This latter fact coupled with the occurrence of pigmentation in some women at the menopause suggests that initially there is an increased demand upon the adrenal cortex which may be imperfectly fulfilled before the gland undergoes hypertrophy

Hypertension The importance and frequency of this is not usually recognized Initially climacteric hypertension tends to be of a labile type and may disappear spontaneously after one or more years but it often progresses to a more severe and permanent type and secondary changes may occur in the vessels Indeed the climacteric may be considered the most important cause of hypertension in women and is probably of pituitary origin In this connexion it is of interest to note that bilateral

ovariectomy or radium castration did not in my cases (see Castration section) produce hypertension This suggests that apart from the influence of ovarian failure on the pituitary gland other changes in that gland occur in the fourth or fifth decade coinciding with the time of the climacteric This theory is also supported by the vasomotor instability and excess of gonadotrophins found at the climacteric age (e g 45) in women castrated many years previously e g 30

Impaired carbohydrate tolerance Only a small percentage of women develop clinical diabetes mellitus at the climacteric but an impairment in a considerable number is shown by routine investigation of carbohydrate tolerance This appears to be due to pituitary overactivity since suppression by large doses of oestrone produces both a normal carbohydrate curve and a disappearance of urinary gonadotrophic hormone disuse of *oestrone being followed* by a return to the original condition The impaired carbohydrate tolerance is not caused by gonadotrophic hormone though carbohydrate tolerance gives a convenient *estimate of pituitary hyperactivity* which in the opinion of the present writer is responsible for a large percentage of diabetes occurring in fat females over 40 Pituitary radiation *or oestrogen therapy* may be then more logical than insulin but the incidence of pancreatic diabetes or the value of insulin in severe cases must not be ignored

The *adrenal* cortex hypertrophy (probably secondary to hypersecretion of the pituitary corticotrophic hormone) may also play a part in climacteric diabetes since the adrenal 11 oxycorticosterones are diabetogenic

Thyroid changes The pituitary hyperactivity is not only gonadotrophic it may spread to its other functions thus producing an excess of thyrotrophic hormone This may initiate exophthalmic goitre at the climacteric or incite an exacerbation of a pre existing mild or latent hyperthyroidism Sometimes a symptomless and long standing goitre or small adenoma is driven into activity with the development of symptoms of toxic goitre (secondary thyrotoxicosis) Climacteric hyperthyroidism may be progressive or there may be a gradual return to normal in mild cases Sometimes *this involution is excessive* and goes on to myxoedema The latter may however appear without an obvious preceding hyperthyroid phase

Breasts After the climacteric the mammary glands tend to atrophy but this may not be visible owing to the deposition of fat which produces a superficial enlargement In the pre menopausal phase of excessive oestrin production the ducts may undergo lengthening and tortuosity occasionally with epithelial proliferation associated with tenseness paraesthesias hyperaesthesia (sometimes erotic) and pain thus cystic masto pathia or so called chronic interstitial mastitis with or without adenomas may develop Occasionally the breasts secrete a thin fluid and this may be explained by the superimposed activity of the pituitary lactogenic hormone (prolactin) which parti cipates in the general hyperactivity of the pituitary as also the prolonged lactation which is sometimes observed in women who become pregnant about the period of the menopause Waves of excessive oestrin production mammary hyperplasia and imperfect involution are predisposing factors to masto pathia cystadenoma and even carcinoma of the breast

Acromegaly Mild acromegaly may be a feature of pregnancy since pregnancy cells are eosinophilic It is perhaps unexpected at the climacteric since basophilic cells predominate at this time Nevertheless mild or fugitive acromegaly does occur and is explicable as resulting from the spread of hyperplasia to the eosinophil cells

Simmonds s cachexia An indefinite or incomplete syndrome with some features of Simmonds s cachexia may be met with at the climacteric particularly when there is a history of multiple pregnancies Perhaps it is more correct to say that a pre existing mild hypopituitarism may be revealed or exacerbated The pituitary gland is unable to satisfy the extra demands made upon it and a phase of hyperactivity is followed by a phase of exhaustion in much the same way as hyperthyroidism may be spontaneously replaced by hypothyroidism Several examples of premature ageing or inexplicable weakness a common feature of the climacteric may have a pituitary basis Loss rather than gain in weight might be expected but even cases of Simmonds s disease proved by necropsy have lacked cachexia

Hypersensitivity to adrenaline This is sometimes met with at the climacteric and Hannon thought that it might be the basis of the vasomotor instability It is also conceivably a factor in

producing hyperglycaemia and hypertension although hyper pituitarism is a more probable explanation

Nervous and psychological disorders Though a tendency towards nervous instability is always present at the climacteric the degree and extent of the changes depend on the pre-existing nervous constitution of the individual Well balanced individuals pass through the climacteric with only minor symptoms, whereas the less stable may develop a severe neurosis or perhaps a psychosis

Anxiety emotionalism nervous tension irritability All these are common characteristics of the climacteric woman and though she often knows that her anxiety has no reason she cannot prevent herself feeling anxious and often this anxiety is projected on to her family with disquieting results The nervous tension is often distressing and the patient says she feels all pent up inside as if she must burst or scream aloud Hyperadrenalism might explain some of the abnormal feelings Insomnia is often troublesome

Vasomotor instability is manifested by hot flushes (vasodilation) often starting in the face and travelling all over the body These may be spontaneous or induced by emotion, and may occur many times a day The face and neck are seen to go a deep red The flushes are often followed by a wave of chilliness (vasoconstriction) and profuse perspiration The blood pressure may fall during the flushes and rise with chilliness Paraesthesia cold extremities tremors palpitations colonic spasm cardiospasm angioneurotic oedema and pseudo angina are other features

Migraine This may be very troublesome at the climacteric Migraine is often influenced by endocrine factors as suggested by its association with puberty menstruation and the menopause and a tendency to disappear during pregnancy lactation and post climacteric life Though often aggravated in the earlier phase of the climacteric many women lose their migrainous symptoms after this period An attack is often preceded by a diminution of urinary oestrone and the appearance of an excess of gonadotrophic hormone Its occurrence at the climacteric might be explained by a vasomotor spasm of the cerebral vessels since cervico thoracic sympathectomy relieves the condition Another explanation is the enlargement of the pitui

tary gland since migraine is a feature of pituitary syndromes with or without neoplasm Timme and Thomson also thought migraine was more common in those women with a calcified suprasellar diaphragm preventing pituitary expansion The pituitary theory is supported by the beneficial effects of large doses of oestrogens which suppress pituitary activity and cause a disappearance of urinary gonadotrophic hormone It is not the latter that causes the migraine since benefit may also result from injections of this hormone which depresses pituitary hyperfunction Alvarez found that an artificial menopause brings relief in nearly half the cases of idiopathic migraine but may make the condition worse

The skin General or local pruritus may be very troublesome and various forms of dermatitis and impetigo occur Pruritus leucoplakia kraurosis and even superimposed carcinoma may affect the vulvar skin and cause much suffering These abnormalities are aggravated by glycosuria but also occur in its absence

Uterine bleeding Menstruation may become irregular occurring more frequently or at longer intervals Menorrhagia may be troublesome If the gynaecologist has excluded fibroids polypi or carcinoma the endocrinologist may postulate anovular bleeding since the urinary gonadotrophins at the climacteric are follicle stimulating and not luteinizing If progesterone and chorionic gonadotrophins fail hysterectomy or radium or radiation may be called for Large doses of stilboestrol are sometimes effective although without obvious rational basis

Sex function This may continue quite normally for twenty or more years after the climacteric Libido may be exacerbated Occasionally atrophy of the vagina or vaginitis causes dyspareunia but this responds to oestrogen therapy

Libido With an artificial menopause loss of libido is rare and there may be some increase Loss may rarely be observed at the natural climacteric although subsequently there may be a gradual waning but not necessarily so It is not easy to differentiate psychological from endocrinological factors

Treatment

The climacteric is largely an endocrine change and when this is too abrupt or excessive the logical treatment is endocrine The object is twofold

(1) Substitution therapy with oestrogens and (2) depression of pituitary hyperactivity the latter fortunately being achieved by the former An alternative is pituitary radiation From a study of the time sequence of oestrone and prolan content of the urine and the appearance and disappearance of symptoms the cause of the symptoms appears to be pituitary hyperactivity The excess of prolan A (follicle stimulating hormone) is only one index of a general pituitary hyperactivity Experimentally oestrogens abolish pituitary castration cells of the ovariectomized rat restoring the histology to normal Most observers find that oestrogen therapy abolishes the excess of urinary gonadotrophins but clinical benefit may be obtained before this occurs and in doses insufficient to achieve the latter

Oestrogen administration in adequate doses will

(1) Abolish vasomotor symptoms especially flushes
(2) Decrease general nervous irritability and anxiety
(3) Frequently ameliorate or abolish migraine
(4) Improve or abolish pruritus pruritus vulvae kraurosis vulvae leucoplakia vulvae senile vaginitis and dyspareunia from vulval atrophy
(5) Decrease hypertension
(6) Improve carbohydrate tolerance

Oestrogens do not appear to influence climacteric adiposity and this is best treated by diet and thyroid in doses which will not produce undue acceleration of the pulse

The disadvantages of oestrogen therapy When it is necessary to control symptoms by large doses certain unpleasant effects may be observed Backache is produced and a feeling of pelvic congestion that is likened to premenstrual discomfort or even to labour Uterine haemorrhage may occur during oestrogen therapy but more usually after its temporary cessation Such *haemorrhage may* be severe and results from a cystic hyperplasia of the endometrium It is comparable to anovular menstruation and supports the theory of inducement by a fall in blood oestrogen Compatible with this is the stoppage of such haemorrhage by resuming or increasing the dose of oestrogen or its avoidance by a gradual reduction of dosage

The breasts may become swollen and painful Experimentally oestrogens produce a cystic mastopathia comparable to

chronic interstitial mastitis, and though the elongation and hyperplasia of the ducts are reversible changes on withdrawing oestrogen, cyst formation may be persistent. In the opinion of the present writer such pathological changes may be produced in the human breast and persist as a result of prolonged treatment with large doses of oestrogens. In rats the epithelial hyperplasia of the mammary ducts may become malignant. Can human mammary cancer thus be produced? Most experimental workers and clinicians answer this question decisively in the negative, on the grounds that the relative dosage and period of oestrogen administration is very much greater in the rat, and that only a cancer-susceptible strain of rat will react. This is probably so, although the dose necessary to control symptoms in woman may be large enough to produce quite obvious hyperplasia of the breast. The possibility of carcinoma of the cervix from oestrogen therapy is even more remote, and according to some non-existent. Zuckerman found that in monkeys the metaplasia of the cervical epithelium that resulted was non-malignant; he also failed to find breast changes.

Dosage of oestrogens. The above considerations suggest that the dose of oestrogens should be the minimum required to control the symptoms adequately. It should be a dose that fails to produce persistent changes in sensation or appearance in the breasts. It could be ascertained with some exactitude by (1) the resulting disappearance of urinary gonadotrophins, (2) the change of the vaginal smear from leucocytes, erythrocytes and deeply staining vaginal oval cells to one showing leucopenia, no erythrocytes and flat cornified cells (oestrus type smear). The disappearance of symptoms is, however, a good clinical criterion.

Oestrogens may be given by mouth, e.g. 1 to 5 mg. stilboestrol, hexoestrol or dienoestrol daily, or 1 to 5 mg. oestradiol benzoate injected intramuscularly twice weekly. Bishop (1938) found a subcutaneous implant of oestrone or oestradiol effective in women, and some climacteric women doctor patients of mine prefer this method of treatment. 30 mg. pellets are often effective for some 6 to 12 months. If bleeding occurs progesterone should be injected. A pellet of progesterone might be implanted at the same time as the oestradiol, although progesterone pellets tend to extrude themselves in some patients.

Drugs. Bromide and valerian or luminal should be given

where nervous symptoms are troublesome. Thyroid is helpful when indicated.

Psychotherapy. Understanding, sympathy, and reassurance by the family doctor proves of infinite value to large numbers, but the psychotherapist is sometimes needed. The climacteric often causes the disruption of many homes, and the husband too should be given to understand the need for forbearance and kindliness. In these enlightened days most women should be able to approach and pass through the climacteric without fear or major disturbance.

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CHAPTER XXXVIII

THE MALE CLIMACTERIC

UNTIL recently the existence of a male climacteric has been regarded with scepticism I have no doubt from my own clinical observations that it exists and occurs some 10 years later than that in women and then is only manifest in some patients and not in others Heller and Myers (1944) have produced considerable scientific evidence to support the diagnosis of a male climacteric namely (1) an increase in the excretion of urinary gonadotrophins comparable to that found after castration and (2) testicular atrophy and degeneration as shown by biopsy

The symptoms are comparable to those found at the menopause namely vasomotor (hot flushes and sweats) psychic (anxiety fussiness irritability instability loss of power to make or abide by a decision and insomnia) constitutional (fatiguability and malaise) loss of libido and/or potency and urinary (difficulty in starting frequency loss of power in urinary stream)

The treatment is testosterone and it is very effective in correctly diagnosed patients The dosage is 50 mg of testosterone propionate injected three times a week or 600 mg of testosterone propionate implanted subcutaneously The latter procedure is reminiscent of the rejuvenation grafts of monkey s testes by Voronoff Although the claims of Voronoff may well have been exaggerated and dramatized my own experience with testosterone implants indicates that the results were not based on imagination It is of interest that as long ago as 1894 Brown Sequard injected himself with testicular extract in an endeavour to produce rejuvenation and ameliorate prostatic symptoms

Testosterone is also said to relieve angina pectoris in older men (Lesser 1942) It produces hypertrophy of the heart in animals but even so the mechanism of its alleged amelioration of angina pectoris is not clear

With regard to its metabolic effects testosterone produces an increase in metabolic rate and a retention of nitrogen electrolytes and water (Jones et al 1941 Abels et al 1944)

Although there has accumulated considerable evidence in

favour of a male climacteric and a positive favourable action of testosterone it would be foolish to assume that testicular atrophy is more than one manifestation of old age or that it is either the cause or the main mechanism of senile degeneration

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CHAPTER XXXIX

SEXUAL PRECOCITY

(Pubertas praecox Macrogenitosomia)

OUTSIDE what may be considered a wide normal range e g 10 to 15 years precocious puberty is a comparatively rare condition especially in the case of true precocious puberty as distinct from pseudo precocious puberty For this reason even a specialist in endocrinology is dependent upon the reports of other observers in order to view the subject comprehensively and it is therefore my intention to supplement a general dis cussion of this disorder by a considerable number of actual case reports illustrating diverse features

Definition

True sexual precocity may be defined as an adult type and degree of gonadal function and secondary sexual character istics occurring in the male or female some years before such development is normally expected Pseudo sexual precocity may be defined as an apparent sexual precocity in children manifested by some secondary sexual characteristics and a hastening of general somatic development but not associated with an adult type of gonadal structure or function The adoption of such a classification is of great help in the under standing of the aetiology and mechanism of sexual precocity

(a) True Sexual Precocity

This may be caused by (i) an idiopathic acceleration of the normal puberty mechanism (ii) a hypothalamic tumour probably operating via the pituitary (iii) a pineal tumour which acts not by virtue of its supposed endocrine function but by a secondary disturbance of hypothalamic function (iv) initial manifestations of pituitary acromegaly and possibly the pituitary type of Cushing s syndrome (apart from these two types a pituitary tumour is not usually found as a cause of sexual precocity nor is there as yet forthcoming evidence of an increase or hyperplasia of the basophil cells or of any chromo phil cells as a cause of sexual precocity) and (v) Albright s

syndrome in girls in which segmental rarefaction of bones and corresponding skin pigmentation may be associated with sexual precocity (see Parathyroid section)

(i) *Idiopathic acceleration of normal puberty* Normal puberty is initiated by the secretion of the gonadotrophic hormone by the anterior pituitary gland and from observation in man and animal experiments we know that the ovaries and testes are responsive to such stimuli even in the first years of life although there may be a short period after birth in which there is relative refractoriness to such stimuli In Novak s series of 9 cases of constitutional precocious puberty 2 menstruated as early as 15 months of age In Escomel s famous case of a Peruvian child who became pregnant at the age of 5 years 8 months and who was delivered of a child by Caesarian section the first menstruation was noted at 7½ months In another case (Mandeslo) menstruation commenced at 3 and pregnancy occurred at 6 years of age These patients not only menstruate but they ovulate as shown by pregnancy and by the observation of corpora lutea during diagnostic abdominal laparotomy There may however be initial periods in which anovulatory menstruation occurs The belief that the mechanism in these patients is normal except for the age factor is based on the fact that after the age of puberty e g 12 they are no different from other girls or later on women and no pathological lesion ever manifests itself In one patient (Haller) menstruation was first observed at the age of 2 and the patient was observed throughout life the menopause occurring at the age of 52 Menstruation is usually regular at intervals of 28 days but initially it may occur at intervals of some months These patients develop secondary sexual characteristics at the onset of menstruation or soon after e g development of the breasts pubic hair of feminine type and axillary hair in some although in others it may not appear until some years later There is never any hirsuties of the face or body The general somatic and skeletal development is several years in advance of the chronological age and that is why pregnancy is not so fantastic in a girl of 6 who looks more like a girl of 16 They grow much more rapidly than other children although their ultimate height may be shorter as the epiphyses may close at the age of 10 The girls may be muscular and strong or may only differ from normality in the chrono

logical discrepancy It is possible that a similar condition is met with in boys but no one has followed a series of cases over an appreciable period of time

(ii) *Hypothalamic sexual precocity* There is no doubt that tumours of the hypothalamus can produce true sexual precocity in both sexes although it is much more common in boys than in girls e g 14 boys and 2 girls in Weinberger and Grant s 16 cases from the literature including their own Repeatedly the mamillary bodies were described as involved or destroyed The posterior hypothalamus is generally affected as distinct from the anterior hypothalamus In 4 cases a suprasellar tumour was present On physiological grounds one is almost bound to conclude that the mechanism of production of the sexual precocity is irritation or stimulation of nerve fibres from the hypothalamus to the anterior pituitary gland which then produces a secretion of gonadotrophic hormone to act on the testes or ovaries and bring them to maturity of structure and function before their time Unfortunately it has not yet been possible to demonstrate an excess of gonadotrophic hormone in the urine or serum but the technique for such quantitative estimation is not yet well developed Another difficulty is the fact that when examined in such cases the pituitary gland has appeared to have a normal histological structure Nevertheless it seems unlikely that any other mechanism could be responsible As to the clinical features in the male the testes as well as the penis are much enlarged and prostatic massage or biopsy will show fully formed normal spermatozoa The interstitial cells of the testes are also well developed The ovaries show follicles and corpora lutea and resemble normal adult ovaries the uterus is enlarged and the breasts developed In both sexes the pubic hair is present and usually profuse but in the boy as well as in the girl its upper limit is horizontal as in the female In the boy there may also be hair in the moustache area but this does not occur in the girl In boys hair may be met with on the thighs and back but more usually it is limited to the pubis and moustache area Hair does not occur on the trunk in girls and is rare in boys Somatic development is precocious in both sexes height weight and epiphyseal development being several years in advance of the chronological age The tendency to premature closing of the epiphyses would however

tend to ultimate dwarfism if the patient lived long enough The patients are not usually fat and adiposity is not a present

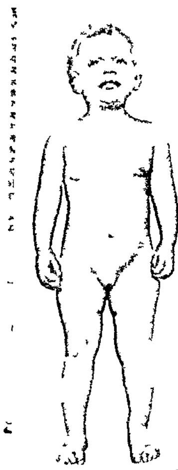


FIG 73 SEXUAL PRECOCITY Girl aged 23 months breast d velopment and wide pelvis vaginal bleeding began at 16 months and recurred at monthly intervals no hair on the trunk except for a few fine hairs in the pubic reg on Laparotomy reveal d both ovar es consid rably enlarged (three times normal for her age) The lower pole of the left ovary was cy t c and mi roscopic examination showed a foll cular cyst with much proliferation of granulosa cells and a sl ght luteal rea tion ova at various stages of maturation but no definite tumour (By courtesy of Dr W B Ellis)

ing feature Muscular development is usually comparable to their advanced physiological age but the Hercules type is comparatively rare This was however present in a high degree

in the remarkable case of Le Marquand (see appendix) The blood pressure is normal or subnormal

Depending upon the size of the tumours neurological features may be absent slight or presenting e g convulsions vomiting ataxia spasticity nystagmus papilloedema optic atrophy and rage and irritability of hypothalamic type The site and nature of the tumour does not appear to permit of satisfactory surgery and even when the patient survives operation the neurological lesions persist or are aggravated Endocrinologically improvement is not usually marked probably because of the incompleteness of the surgical intervention The prognosis therefore is poor

Under the heading of hypothalamic sexual precocity might also be considered that following encephalitis or meningitis Ford and Guild described two cases in girls age 7 and 9 following measles encephalitis and one in a boy of 12 following encephalitis lethargica This boy was sexually aggressive towards girls and women They also refer to other cases in the literature following meningitis and chronic tuberculous meningoencephalitis There may be a latent period of several years following the infection before symptoms of sexual precocity are manifest and this may be due to the gradual development of secondary hydrocephalus A more direct and immediate involvement of the hypothalamus by the infective process is also probable

(iii) *Pineal tumours* The pineal gland is a small conical body attached by a short stalk to the roof of the third ventricle and according to Starling represents the remains of a primitive dorsal invertebrate eye It consists of neuroglial cells and other cells of two types one containing fine acidophil granules and the other basophil granules There is no confirmed experimental evidence that extracts of the pineal gland have an endocrine function and it is now generally believed that pineal tumours produce sexual precocity by virtue of the mechanical interference with the hypothalamus the mechanism being the same as described in the previous section It has always been recognized that pineal tumours produce sexual precocity only in boys and we have seen in the previous section that hypothalamic tumours produce sexual precocity predominantly in boys The symptomatology both endocrinological and neurological is that of hypothalamic sexual precocity The literature

and a case of sexual precocity associated with a teratoma of the pineal body are described by Gerstley and others (1940)

(iv) *Pituitary type* All true sexual precocity involves a pituitary gonadotrophic stimulus in so far as present physiological knowledge is applicable but by pituitary type of sexual precocity is meant a type in which the sexual precocity is part of a definite pituitary syndrome associated with a pituitary lesion Some endocrinologists have queried whether such a type exists and the evidence for the condition is usually forthcoming in incomplete familial types of mild acromegaly and mild Cushing s syndrome Both acromegaly and Cushing s basophilism syndrome are associated in their fully developed state with impotence or amenorrhoea but in the early phases of those cases starting in the few years before puberty evidence of an initial period of premature sexual development is in my experience met with This was also found to be the case by Cushing Pardee and Farber In Cushing s syndrome associated with an adrenal tumour pseudo sexual precocity involving facial hirsutism and somatic development has been encountered (Crooke and Callow)

(v) *Albright s syndrome* This syndrome consists of multifocal areas of osteitis fibrosa and patchy cutaneous pigmentation both of segmental distribution but not associated with evidence of hyperparathyroidism and when occurring in children it is associated with sexual precocity In Albright s original description he stated that sexual precocity was only observed in girls but Falconer and Cope later reported sexual precocity in a boy In both sexes the sexual precocity is true and complete and associated with precocious somatic and skeletal development The syndrome is discussed in the Parathyroid section The aetiology remains undetermined

(b) Pseudo-sexual Precocity

The precocity may be manifested by increased somatic and skeletal development by secondary sexual characteristics or by some primary sexual characteristics but the complete picture of puberty in all its aspects is never present The lesion may be adrenal ovarian testicular or thymus

(i) *Adrenal* The lesion may be either an adrenal cortex tumour innocent or malignant the latter being more frequent

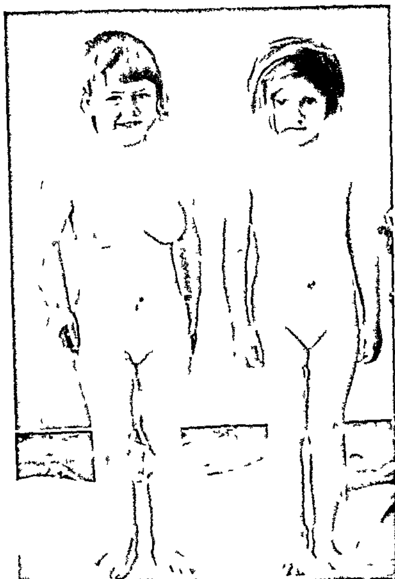


Fig 74 Sexual Precocity Girl aged 5 (with control same age) multiple cystic ovaries without corpora lutea partial resection of ovaries shown by laparotomy a year later to have been followed by regeneration and new formation of large cysts Sub total bilateral ovariotomy without fundamental influence on the condition which is primarily of hypothalamic pituitary origin (By courtesy of Dr David Navarro who referred the case to the author)

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and sexual behaviour is attempted but the testes are infantile and spermatogenesis does not occur

It is of especial interest to note that in some cases plethora polycythaemia hypertension (220/110) and other features of Cushing s syndrome are met with and in reading through the older literature one encounters frequent references to a plethoric countenance In Wilkins s boy of 3 the patient had signs of adrenal insufficiency e g pigmentation of the skin and gums a low blood sodium and a dramatic craving for salt In this case at autopsy the adrenal cortex was composed largely of androgenic or pre natal zone cells which apparently replaced other elements of the cortex and the testes were large and composed of similar cells

In the absence of metastases successful removal of an adrenal tumour will produce a reversion to normal

(ii) *Granulosa cell tumour of the ovary* This type of tumour is not really rare Meyer describing 33 cases in 1931 and Pratt collected records of 200 in 1937 but it is rare in children Some 30 per cent are said to be malignant but complete cure by removal is claimed in 60 per cent of cases The tumours are usually unilateral but may be bilateral Sexual precocity may show itself as early as the first year of life In addition to menstruation and precocious development of labia majora vagina uterus and breasts (which may be pigmented) the general somatic and skeletal development is far in excess of the chronological age Premature union of the epiphyses occurs Pubic and axillary hair develops but there is no hirsuties or acne Apart from the essential absence of ovulation and corpus luteum formation the sexual precocity has all the other features of a true sexual precocity It is interesting that although the excessive oestrogen is secreted by a granulosa cell tumour its amount appears to have a rhythmicity which may be monthly or more irregular the menstruation period being associated with enlargement and turgescence of the breasts Biological assay shows that the tumour tissue and the urine contain a considerable excess of oestrogens

As to pathology the tumour cells resemble the normal granulosa cells of the Graafian follicle In certain sections the cells may assume a follicle like structure and in others the disposition may be in the form of cords or strands

or an idiopathic cortical hyperplasia Sometimes one meets with an embryonic adrenal rest (collection of cortical cells) in the abdomen pelvis or ovary or numerous adrenal rests scattered throughout the abdomen and pelvis Both sexes may be affected although the condition is more frequently met with in girls

The symptoms may occur in the first year of life or may not appear until the age of 10 The adrenal cortex tissue secretes a large excess of androgens which may be assayed as 17 keto steroids in the urine For example values of 40 mg per day may be found whereas normal children before puberty show less than 5 mg per day and sometimes mere traces and normal adults excrete only 10 to 15 mg In most cases and in both sexes these androgens produce not only pubic hair but also hair on the body and on the face including the cheeks and perhaps forehead This hirsutism always justifies a probable diagnosis of an adrenal cortex hyperfunction although such a lesion is not necessarily the only or primary lesion However even with an adrenal tumour some children in the first years of life do not show any evidence of hair on the face or trunk as distinct from vulval or pubic hair and the absence of hair does not necessarily exclude an adrenal tumour Probably there is in such cases an absence of responsiveness of the dermal tissue to the androgen stimulus Another result of the excess of androgens is acne on the face and perhaps on the body

In girls it is rare for menstrual bleeding to occur before the age of 9 or 10 but exceptionally it may occur in the first or second year of life The clitoris is usually but not invariably grossly enlarged and there may be a close resemblance to pseudo hermaphroditism In fact this depends upon whether the excessive androgenic secretion has started before or after birth and in this connexion it is interesting to note that a boy of 3 with sexual precocity had a sister who was a p eudo herma phrodite (Wilkins et al 1940)

The precocious somatic and skeletal development and the enormous muscular strength of these children especially in the boys (Hercules type) must also be ascribed to the excessive secretion of androgens Although they grow rapidly they are ultimately dwarfs if they live because of premature union of the epiphyses In the males the penis is big erections occur

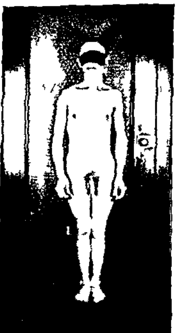






Fig 5 *Idiopathic Sexual Precocity* Father aged 33 and two sons aged 8 and 4 years the children showing the sexual precocity as did the father at their age The condition here therefore is idiopathic and familial (By courtesy of Dr H I Rush *Endocrinology* 1937 xxi 3)

Occasionally a teratoma of the ovary will produce sexual precocity and clinically the latter appears to be of similar type to that produced by a granulosa cell tumour A summary of Harris s case is appended showing complete recovery 8 years after removal of a malignant teratoma

(iii) *Interstitial cell tumours of the testis* These tumours are very rare but occur both in adults and boys In adults they have no dramatic manifestations, but in boys usually after an initial 5 years or more of normality they produce full puberty in some months Since the tumours consist almost entirely of interstitial cells of Leydig they act in all probability by secreting large quantities of testosterone In one adult case the tumours were bilateral and a similar tumour occurred in the brother of the patient (quoted by Stewart and others 1936) but in children the reported cases have been unilateral The penis becomes of adult size or larger and erections occur but no emissions Unlike other types of sexual precocity e g adrenal or hypothalamic there is usually no attempted sexual gratification with girls or women and no aggression or violence The muscular development however is very great and quite as Herculean as that associated with adrenal tumours Somatic and skeletal growth is accelerated but premature union of epiphyses results in ultimate dwarfism The pubic hair is of male pattern and hair occurs on the body and on the face a full moustache and beard being present in Sacchi s case It is interesting that the pubic and body hair should be of male type compared with the female type of pubic hair and absence of body hair in hypothalamic sexual precocity Probably the amount of testosterone secreted by an interstitial cell tumour is much greater than that secreted by the prematurely developed testes of hypothalamic cases Removal of the testicular tumour usually produces a regression in sexual development although somatic development remains In Rowland s case of a boy aged 9 there was no appreciable regression 2 years later but at that time normal puberty may have followed on

(iv) *Thymus tumours* Leyton described a case of pseudo sexual precocity in a boy of 11 apparently due to a thymus carcinoma and associated with clinical features of Cushing s syndrome However the genitalia were normal and pubic hair was absent In fact a superficial appearance of sexual precocity

subnormal through such premature union It is also a fact that many normal girls cease to grow at puberty This is rarely so in boys so that the amount of testosterone secreted in normal puberty is rarely sufficient to produce union of the epiphyses of the long bones for some years afterwards e g 17 or 18

Diagnosis

In girls sexual precocity without pathological features may be idiopathic or constitutional but it is well to bear in mind that a small hypothalamic lesion may reveal itself later on A hypothalamic or pineal tumour may first manifest itself neurologically by optic atrophy or papilloedema nystagmus convulsions vomiting ataxia spasticity rage and irritability Exact localization is rarely possible before cerebral exploration is undertaken The sexual precocity associated with a hypothalamic or pineal tumour is of a physiological type except that it is chronologically premature It may occasionally be associated with diabetes insipidus

Ovarian granulosa cell tumours or rarely ovarian teratoma also manifest themselves in physiological type except that ovulation does not occur They are often palpable on pelvic examination Interstitial cell tumours of the testes are palpable in the scrotum Their manifestations would be physiological except for the absence of spermatogenesis and the chronological age

Adrenal cortex tumours should always be suspected in girls if there is a growth of hair on the face and body as distinct from the pubis and if acne is present The rule however is not invariable and abnormal hair growth may not be present especially in the first few years of life It is also generally noted that girls with adrenal tumours do not menstruate before about the age of 9 as distinct from hypothalamic or granulosa cell tumours which may produce menstruation in the first few years or months This rule however is not absolute and in some girls with adrenal tumours menstrual bleeding has occurred in the first few years of life The clitoris is nearly always enlarged with adrenal tumours as distinct from other varieties of sexual precocity in girls but this is not invariably so

In boys hypothalamic or pineal tumours produce pubic hair of feminine type and usually only a slight moustache whereas adrenal tumours tend to produce hair on the whole body pubic

was due to a moustache and hair on forehead and between eyebrows

The adrenal cortex was hypertrophic and an excessive secretion of androgens by the adrenals may reasonably be assumed The condition is discussed further under Thymus section

Precocious Somatic and Skeletal Development

This occurs in all forms of sexual precocity both true and pseudo types but it varies in degree and as far as muscular strength is concerned with the sex In general however the muscular development and the skeleton is that of a child many years older or it may be comparable to that of an adolescent or adult Thus when pregnancy occurs in a 6 year old girl it is not so surprising as might be the case since she may have the general appearance of a girl of 16 or more years Although the girls are obviously much stronger than others of their chronological age yet it is only in boys that one meets with excessive strength to which the name Hercules type has been given Thus the normal differences in muscular strength between the sexes is accentuated in these pathological types of sexual precocity

The cause of the increased muscular strength must be due in the majority of cases to testosterone or other androgens secreted by interstitial cell tumours or by the adrenal cortex In the case of hypothalamic pituitary sexual precocity in the male the interstitial cells are brought to function in advance of the normal time for puberty and so there is increased muscular strength relative to the chronological age but this strength is rarely of the pathological intensity met with in tumours of the adrenal cortex or of the interstitial cells of the testis Normally at puberty there is a great increase in muscular strength and athletic achievement in boys and this is almost certainly due to the functioning of the interstitial cells This is generally less true of girls and it is therefore not surprising that granulosa cell tumours do not produce that excessive degree of muscular strength in precocious girls

Skeletal growth however is very rapid in both girls and boys and in all forms of sexual precocity It seems therefore as if either oestradiol or testosterone can produce acceleration of skeletal growth and also that either can produce premature union of the epiphyses since the ultimate height is frequently

were removed There was however no recession of the precocious sex change Section of the removed ovary showed normal adult ovarian tissue She came under Dr Novak s attention at the age of 10 having continued to menstruate regularly at 4 weekly intervals since the age of 4 The general appearance was that of a girl of 15 her height was 56 in and her weight 105 lb X ray studies of the bones showed the epiphyses already closed so that although she had grown rapidly her ultimate height would be subnormal B M P was minus 21 per cent urinary oestrogen 25 rat units per day Abdominal laparotomy showed the remaining ovary to contain follicles one corpus luteum and pittings of the surface indicating previous ovulation

2 *Hypothalamic sexual precocity* *Weinberger and Grant s case* This concerned a boy of 7 years 11 months who was normal until 6½ years of age He then began to grow rapidly and to develop adult sexual maturity The testes penis and prostate were of adult dimensions when seen and prostatic massage gave seminal fluid containing motile spermatozoa He had pubic hair but with feminine horizontal upper limit and a fine moustache There was no hair on the trunk He had frequent erections but was not known to masturbate His intelligence was average for his age and so was the behaviour pattern He was 58 in tall compared with a normal of 49 in There was no evidence of Herculean characteristics His hands and feet were larger than normal Cerebral involvement was shown by vomiting torpor and sleepiness tremor of hands headaches staggering gait and papilloedema There was no adiposity diabetes insipidus or polyphagia B.M R was minus 30 B P 100/60 blood sugar 60 mg per cent At operation a glioma of the posterior part of the hypothalamus and third ventricle was removed No adequate follow up is reported but secondary sexual characteristics remained As regards hormone analysis before operation it is interesting to note that it was not possible to demonstrate an excess of gonadotrophic hormone which however was almost certainly present Oestrogens in the urine were normal and androgens (40 i u) four times the normal for a child of 7 (normal about 8 to 10 international units)

Wyllie s case This was a boy of 8 years presented as an example of diabetes insipidus due to a tumour in the region of the pineal gland proved to be a benign glioma He however had a large penis and testicles and some pubic hairs of female type His body was slim and although he is said to have had an adult formation of musculature he was certainly no Hercules His voice was gruff He died after operation

Poston and Barber s case This was a mentally defective boy of 19 months who had a large penis and testes and a few pubic hairs Although the clinical description is inadequate it is included because an autopsy following operation showed an astrocytoma the size of a walnut originally in the left corpus mamillare an apparently normal pituitary gland and normal suprarenals The androgens in the urine were not increased in the only estimation undertaken

hair of male triangular pattern and a strong moustache Interstitial cell tumours may in these manifestations resemble adrenal tumours but sometimes the hair although of male pattern is not abundant Acne is more noticeable with adrenal cortex and interstitial cell tumours than with other types of sexual precocity All these general rules however are capable of considerable variation and all possible lesions must be borne in mind In doubtful cases abdominal laparotomy is justified

Treatment and Prognosis

Idiopathic or constitutional female sexual precocity may continue without harm into adult life Safeguards against pregnancy should be considered Where a cerebral lesion is probable or certain its removal should be considered but the surgical results are not good and some form of persistent or resulting neuroglial disability is not infrequent neither is the sexual precocity necessarily ameliorated since removal is often incomplete or a further hypothalamic lesion is involved in the surgical procedure

A granulosa cell tumour should be removed and cure usually results In one case a recurrence of symptoms led to the discovery of another granulosa cell tumour in the other ovary A malignant teratoma of the ovary has been removed with excellent permanent results An interstitial cell tumour of the testis should be removed and the results are usually good Malignancy is rare

If an adrenal cortex tumour is removed before malignancy has supervened a complete reversion to normal usually follows and even malignant adrenal tumours have been removed with similar favourable results Where bilateral hyperplasia of the adrenal cortex is the apparent cause the prognosis is poor and it is doubtful if surgery can offer any real help but there is rarely any danger to life

(c) Examples of True Sexual Precocity

1 *Idiopathic or constitutional true sexual precocity* Neal's case This patient a girl began to menstruate at the age of 4 and at about the same time the breasts exhibited marked hypertrophy and there developed an abundant growth of pubic and axillary hair At the age of 5 the patient was operated upon at another hospital with a pre operative diagnosis of granulosa cell tumour and the left tube and ovary

but horizontal in its upper border as in the female Hair was present on the outer aspects of the legs and on the back At the age of 3½ he pushed his father's motor bicycle and sidecar out of the shed At

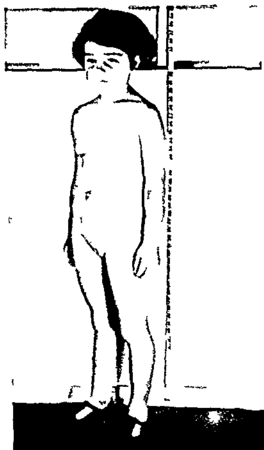


Fig 76 (b)

operation an apparently normal adrenal gland and one testis were removed At the age of 4½ he had the height and weight of a boy of 11 but epiphyseal development was so advanced that Le Marquand concluded he would have been a dwarf with a long trunk and short legs He died at the age of 4 years 10 months from rheumatic endocarditis At autopsy a tumour (astrocytoma) of the interpeduncular space adjacent to the corpora mammillaria was found The pineal gland was normal and there was no internal hydrocephalus The pituitary body examined by serial section appeared normal The suprarenal glands

Le Marquand's case This was a male child whose testes and pubes developed rapidly in size at the age of 14 months and at the same time pubic hair began to grow At the age of 22 months he began to attack

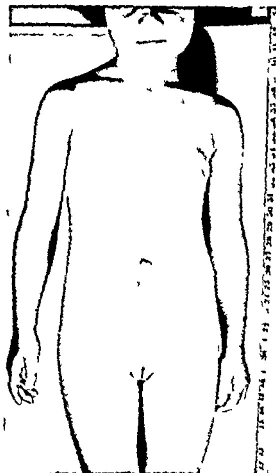


Fig 76 (a)

Fig 76 Idiopathic Sexual Precocity In a girl of 5½ laparotomy showed multiple follicular cysts of the ovaries considerable enlargement of the uterus normal adrenal glands bone age that of 11 years (By courtesy of Dr T E D Beavan)

adult women and rub his erected penis against their legs He showed no interest in little girls In the next 2 years he grew rapidly and developed great muscular strength He showed great motor activity restlessness and bad temper He was not fat The genitals became half the adult size and the voice gruff The pubic hair became abundant

The uterus was palpable per rectum No prostate could be felt and the mammae were not developed The pelvis was of masculine shape and the degree of ossification of the bones at the wrist corresponded to that of a normal child of 3 years of age A tumour could be felt in the abdomen under the left costal margin It was removed when the child was 2 years and 2 months of age It was apparently surrounded by a fibrous capsule and presented a variegated appearance on cross section Some parts of it were necrotic others resembled in structure the normal suprarenal gland but some of the cells were more irregular in size and shape and contained several nuclei Two months after the operation there was a striking improvement in the appearance of the patient the cheeks bulged less the skin of the face had become smooth and child like and all the abnormal hair had disappeared except for a few short dark hairs on the labia majora The labia and mons projected less the clitoris was perhaps smaller and the trunk and limbs were less bulky but the voice remained deep and hoarse Even 2 years after the operation the clitoris was abnormally large and the voice was still masculine

Walters and Kepler's case A girl aged 23 months was referred to the Clinic by Dr R K Dixon of Denver Colorado who had made a diagnosis of probable adrenal cortical tumour She had been delivered at full term by Caesarean section Her mother said that she had always seemed to be somewhat mentally precocious At 18 months she had begun to show precocious physical development She fed herself went to bed alone and acted like a child of 4 or 5 years At the same time it was noted that the labia and clitoris were becoming larger and that black hair was appearing on the labia majora The child began to grow rapidly her shoulders broadened and she increased in height At 23 months she was able to exchange dresses with her sister then aged 5 years although the sister's clothes had to be shortened somewhat It was then noted that the patient's hands were about as large as her sister's On December 12 1936 there was marked vaginal bleeding lasting one day The patient was then 19 months old For 6 weeks prior to admission a little acne had been noted on the forehead and a few weeks prior to admission the child had developed a sense of modesty and had objected to being nude at home or in the examining room and insisted on going to the bathroom alone On examination the child was found to be 37 in in height and weighed 30 lb She appeared definitely larger and heavier than a normal girl of her age Blood pressure was 116/70 The labia majora and minora were well developed Hair was present on the labia and there was a definite disproportionate enlargement of the clitoris There were no laboratory findings of significance except that roentgenograms of the extremities showed the bone age to be approximately 5 years There was no sugar in the urine The urine was assayed for prolan and oestrin with entirely negative results On March 23 1937 a tumour weighing 45 gm and measuring 5 5 × 4 5 × 4 cm was removed from the left adrenal gland (A portion of the adrenal cortical tumour was extracted for oestrogenic substances but none was found) The post operative convalescence was

appeared normal The hypothalamic nuclei appeared normal The pancreas thyroid and parathyroid glands appeared normal The testes contained conspicuous groups of interstitial cells and tubules containing spermatids and spermatozoa

Flicker's case A girl of 3 showing sexual precocity from the age of 18 months when her breasts began to enlarge and her external genitalia developed so that they assumed the character that might be expected at puberty Apart from these features and fatness her presenting symptoms and signs were neurological ataxia nystagmus and optic atrophy A pineal tumour was apparently suspected but a large cyst of the third ventricle was found and tapped However at the age of 7 primary and secondary sexual characteristics were said to be of adult type and personality revealed thalamic outbursts of laughing and crying

Clark Beattie Riddoch and Dott's case The patient a female infant began to menstruate regularly at the age of 6 months At the age of 4 years she had all the bodily characteristics of a mature woman She was 9 in above normal height There were mental precocity in certain directions and secondary sexual characteristics of a psychic order At biopsy the presence of mature follicles and corpora lutea was demonstrated in the ovarian material Death occurred in the sixth year from a streptococcic infection Autopsy disclosed a tumour in the interpeduncular space attached to the mamillary bodies and to the area between them and the tuber cinereum There was no hydrocephalus and the pineal body was intact

Examples of Pseudo Sexual Precocity

(1) *Adrenal*

Collett's case This was an interesting case in a female child of 2 years who came of healthy stock and was the youngest of a family of five normal children Pregnancy and birth were natural but at the age of 9 months the child had a bad attack of pertussis and at 11 months bronchitis and convulsions Between 6 and 8 months a growth of hair was noticed by the parents in the region of the vulvae this gradually became thicker and spread to the limbs and trunk when the child was about 13 months of age At the same time she became heavy and fat grew rapidly and the voice became deep and rough When seen at the age of 18 months the child was considerably taller and heavier than the average her head was large her cheeks bulged and her limbs were short and thick but her hands and feet were well formed Her voice was deep and rough often rising to a squeak as in a boy at the time of the change of voice There was an abnormal growth of hair on the labia and mons veneris with a horizontal upper limit and a dark growth on the thighs shoulders and back Some hair had also appeared on the cheeks The labia majora and mons were well developed the clitoris was a penis like organ measuring 1 5 cm in length with a well developed glans surrounded by a corona and covered by a prepuce which extended into the labia minora There was a urethral groove on its under surface

eighth month and in the ninth month pubic hair appeared The breasts enlarged with each bleeding and the baby was irritable for some days A pelvic lump was felt on examination and a left ovarian granulosa cell tumour was subsequently removed with a return to complete normality

The case is remarkable for its incidence in the first year of life and for its successful treatment The urinary oestrogens were assayed as 66 mouse units *per diem* before operation and nil afterwards

Bland and Goldstein s case This was a child who commenced to menstruate at the age of 7 and at the same time developed large breasts and pubic and axillary hair It is noteworthy that radiograph of the long bones showed the epiphyses to be united some 10 years before the normal time A left ovarian granulosa cell tumour was removed and no menstruation occurred in the next 18 months when the syndrome recurred A similar tumour found on the right side was then removed Menstruation ceased but pubic hair and large breasts remained

(2a) *Teratoma of the Ovary*

Harris s case This is an interesting example of somatic and sexual precocity in a girl of ␣ years with complete recovery after removal of a malignant teratoma of the ovary The child was normal in the first few years of life and then grew very rapidly She had 6 menstrual periods at monthly intervals The breasts became large and the nipples pigmented Axillary and pubic hair developed A small tumour was palpated abdominally and was removed It proved to be a malignant teratoma and contained embryonic lining tissue neuroglial tissue gastro intestinal tissue cartilage dermoid cysts with hair and sebaceous and sweat glands The larger part of the growth consisted of an adeno carcinoma

Unlike most other cases there was no recurrence of growth and the child was quite normal when seen 8 years later

(3) *Interstitial Cell Tumours of the Testes*

Sacchi s case A boy normal until the age of 5½ then rapidly developed puberty—hair on the body pubes and face enlargement of penis deep voice and rapid muscular and skeletal development At the age of 9 he had the appearance of a strong muscular young adult Photographs look like a muscular but short adult with masculine type of pubic hair hair on the chest and a fully developed moustache and beard Mental development was not precocious Erections were frequent An enlarged left testis was removed and 4 months later eroticism and secondary sexual characteristics had disappeared

Stewart s case At the age of 4 the patient gradually developed sexually and somatically the genitals and secondary sexual characteristics attaining adult quality Mental age was 5 A small tumour palpable in the right testis was found to invade it and the whole testis was removed The penis did not decrease in size but sexual eroticism and hair disappeared Microscopic sections showed cords and solid sheets of cells

uneventful and the patient left hospital on the tenth day post operative On July 13 1937 she was examined by Dr Dixon and found to be in excellent condition She then weighed 30 lb and was 38 in in height The pubic hair had changed very little There had been no further suggestion of menstrual bleeding It was observed that the child did not eat as heartily as she had done before operation

Marks Thomas and Warkany s case This case of a girl who died at the age of 1 year 3 days from cardiac failure and pulmonary oedema is of special interest in that the patient had many features of Cushing s syndrome The child was normal at birth and weighed 6½ lb It was breast fed for 11 months At the age of 3 months her appetite became ravenous and she began to gain weight rapidly and became monstrously fat Her cheeks became red and congested the legs cyanotic and mottled and the voice harsh Brown hair appeared on the vulva not on the pelvis and some on the back of the trunk The hair of the head was normal The blood pressure was systolic 220 and diastolic 110 mm of Hg At autopsy a right adrenal tumour and normal left adrenal were found The pituitary gland was normal and the thymus small The ovaries and uterus were normal and the clitoris not enlarged

Fraser s case This boy was normal until the age of 6 months when the penis began to enlarge rapidly and by the twelfth month equalled that of a man of 18 years Erections of the penis were almost constant and masturbation took place frequently the child also rubbing his penis against the mother His testicles however were very small Pubic hair appeared sparsely and acne developed on the face His voice became deep pitched His muscular development was excessive (Hercules type) and his mother was quite unable to control him He ate three times the amount of food normal for his age and increased in weight tremendously His bone age was 5 years and dentition age 3 years Although he had no trunk or facial hair and no radiographic depression of the renal calyces after uro electan an adrenal lesion was thought of and an assay of urinary 17 ketosteroids confirmed this 28 mg per day compared with less than 5 mg for a normal child A right adrenal tumour was removed and the child died the next day The left adrenal was normal The thymus was normal The testes were immature and showed no signs of spermatogenesis

Adams s case This was a boy of 14 years in whom after a normal childhood signs of puberty appeared at the age of 10 From this age although his height did not increase (probably the epiphyses united) he developed great muscular strength excelled in athletic sports and defeated all competitors For 2 years his complexion had been observed to be plethoric and dusky His appearance was that of a sturdy little man He had shaved daily since the age of 12 An adrenal tumour was present

(2) *Granulosa Cell Tumours*

Hall s case The child was normal at birth except for a crop of luxuriant hair on the head Menstrual bleeding occurred in the seventh and

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Mandeslo (1658) quoted by Lenz J (1913)
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separated by small connective tissue septa The cells were large the *nuclei compact and the cytoplasm spongy*

Sutherland's case A boy of 11 with a large tumour of the right testis showed adult primary and secondary sexual characteristics great muscular development premature union of the epiphyses and short stature The pubic hair from the photograph is seen to be of male type ascending towards the umbilicus in triangular fashion The tumour was removed and consisted of interstitial cells

Rowland's case This boy was normal until the age of 6 when he developed signs of puberty At the age of 9 he appeared to be an almost fully grown man of 18 being 5 ft tall very powerfully built and having much hair on the chest loins and pubis (male type) His intelligence was above the average for his age he was good tempered and not vicious in any way this being unlike many of the subjects of premature puberty due to other causes He was very fond of his young brothers and sisters but he disliked and avoided older girls His mother had never noticed any signs of nocturnal seminal emissions A large tumour destroying and replacing the right testicle was removed and found to consist of interstitial cells Two years later he was readmitted for acute appendicitis and there was then no retrogression in the signs of puberty (This paper also includes a report and photographs of Sacchi's case provided by Dr Parkes Weber)

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have a testis on the right and an ovary on the left with masculine plumage on the right half of the body and feminine plumage on the left half of the body This means that one half of the body is genetically determined to have a responsiveness to androgenic hormone and not to oestrogenic hormone and vice versa since the secretion of both gonads are circulating throughout the body Similar responsiveness and refractoriness although not unilateral is seen in human hermaphrodites These conceptions become of general importance when it is remembered that testis and ovary both secrete androgenic and oestrogenic hormones (see Physiology section)

Clinical

True hermaphroditism is a rarity and is unlikely to be met with by the majority of readers of this book In fact less than twenty well authenticated cases have been recorded Owing to the unpredictable responsiveness or refractoriness of tissues to circulating hormones the external appearance may be predominantly male or female or obviously mixed This is also true of the sexual and secondary sexual organs as well as of the emotional and psychological attitudes which do not necessarily correspond to the predominantly genital or physical characteristics

Young described a man of 20 an excellent athlete 6 ft tall and weighing 144 lb with normal male hair on the body and face and with a well developed penis who was operated upon at the age of 20 for a tender mass in the left groin clinically believed to be an undescended testis The contents of the hernial sac presented however a small uterus and a normal ovary and fallopian tube all of which were removed A biopsy of the right scrotal testis showed interstitial cells of Leydig and seminiferous tubules which however did not contain any spermatozoa The patient had normal masculine sexual feelings and potency and passed through a normal boy s puberty The only abnormality of the external genitalia apart from an undescended testis was the presence of hypospadias a condition *which can be experimentally produced in male rats by* injecting the pregnant mother with oestrogens (Green Burrill and Ivy 1940)

A different type of true hermaphroditism predominantly

CHAPTER XL

HERMAPHRODITISM

Definition

THE term hermaphrodite is derived from Greek mythology being the composite name given to the bisexual child resulting from the celestial union of Hermes and Aphrodite Hermaphrodite is frequently depicted in Greek sculpture as being a beautiful woman with well developed busts but with good muscular development and the external genitals of a male

The scientific definition of a hermaphrodite (i e true and not pseudo hermaphrodite) is an individual having both a testis and an ovary, or a composite ovo testis on one or both sides The external appearance of such an individual may be predominantly male or female or obviously intersexual

Aetiology

The cause of hermaphroditism is unknown and the adrenal cortex hyperplasia sometimes met with is concomitant and not aetiological It is interesting to recall that hermaphroditism is normal for some of the lower species e g the worm and that it is not infrequently met with in pigs and goats The hen is potentially hermaphrodite as the right gonad is rudimentary and will become a fully functioning testis if the left ovary is removed The change of sex in the hen may be so complete that the mother of chicks may become the father of chicks This remarkable transformation is perhaps less difficult to appreciate if it is remembered that the medulla of the ovary is the homologue of the testis Embryologically in man the mass of cells on the genital ridge which will become the ovary or testis cannot be differentiated before the embryo has reached the seventh week of development Whether the central portion (or medulla) of this genital mass of cells develops into a testis or the outer area (cortex) develops into an ovary or both develop equally to form an ovo testis is no doubt determined by genetic or chromosomal influences The importance and possible unilateral influence of a genetic factor is well illustrated by the bullfinch which may

have a testis on the right and an ovary on the left with masculine plumage on the right half of the body and feminine plumage on the left half of the body This means that one half of the body is genetically determined to have a responsiveness to androgenic hormone and not to oestrogenic hormone and vice versa since the secretion of both gonads are circulating throughout the body Similar responsiveness and refractoriness although not unilateral is seen in human hermaphrodites These conceptions become of general importance when it is remembered that testis and ovary both secrete androgenic and oestrogenic hormones (see Physiology section)

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A different type of true hermaphroditism predominantly

female was described by Seligman, Krusshar and Byron (1941). At birth the genitalia consisted of an apparently normal vulva and protruding therefrom an organ resembling a penis about 2½ cm long. There was no urethral opening in this organ. The child was brought up as a girl. From the age of 13 she experienced abdominal cramps and nausea each month, but apart from one slight bleeding in her thirteenth year and again in her fifteenth year there was no menstruation. At the age of 17 she sought advice because of a large penile-like organ of male dimensions which erected frequently and pleasurably. The urethral opening was not in the penis but in the vestibule. The labia were normal and the vaginal orifice admitted two fingers. Her psychology remained essentially female, and she had a male friend. However, she was tall, thin and flat chested, with male type breasts and skeletal form. She had a little hair on her upper lip, and hair on the pubis, axillae and legs. Abdominal laparotomy revealed an infantile uterus and Fallopian tubes. Two gonads appeared small, and a wedge resection from each revealed an ovo-testis showing on histological section: (1) ovarian tissue with degenerating primordial follicles, (2) testicular tissue with well defined interstitial cells and seminiferous tubules without spermatozoa, and (3) cords and strands of large mononuclear cells which resembled adrenal cortex tissue. The gonads (ovo-testes) were removed and the penis amputated. Oestrogens were administered with resulting gain in weight, fat deposition and feminine contour, breast development, and essentially feminine outlook and habits.

Diagnosis

This is usually made after operation for an inguinal lump, or after exploratory abdominal laparotomy.

Treatment

This depends upon both the external configuration and the emotional psychological attitude. The gonad corresponding to the latter is usually retained and the other gonad removed. Appropriate reconstruction of the external genitals, such as removal of penis (or hypertrophied clitoris) and dilatation of vagina, or repair of hypospadias are carried out. In the case of an ovo-testis it might be advisable to remove both gonads and

administer oestrogens or androgens Each patient needs individual consideration

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PSEUDO HERMAPHRODITISM

Definition

Pseudo hermaphroditism is a condition in which there is only one type of gonad testis or ovary but in which the external genitals are a mixed representation of male and female characteristics or characteristic of the opposite sex to the gonads The term should be applied only to those cases in which the condition is present from birth and not to those instances of virilism or feminization which appear in later life It is also not intended to include under this heading sexual precocity in the female due to an adrenal tumour and associated with hirsutism unless some clinical abnormality was present at birth Classification according to the type of gonad is the simplest i e testicular pseudo hermaphroditism and ovarian pseudo hermaphroditism

General Considerations

In both types of pseudo hermaphroditism the external genitals are partly male and partly female and the predominance of male or female external characteristics does not necessarily indicate the nature of the gonads If the latter are palpable in the perinaeum or scrotal sac or labial folds or in the region of the inguinal canal they are more likely to be testes than ovaries but this cannot be assumed Ovaries are usually but by no means invariably intra abdominal and many surprises will be met with on laparotomy

In both types the general habitus and skeletal development tends to be male but a gynaecoid pelvis and female gait can be present with either testes or ovaries The ovarian pseudo hermaphrodites are usually stronger than normal females and

the testicular pseudo hermaphrodites usually weaker than normal males A testicular pseudo hermaphrodite may have less hair on the face than an ovarian pseudo hermaphrodite Mistake in the sex of the child is common In the adolescent or adult phase ovarian pseudo hermaphrodites tend to have a female libido and sexual behaviour and rarely function as male The testicular pseudo hermaphrodite may function as male or female or as active or passive homosexual according to genetic tendencies upbringing or anatomical genital configuration

In both types fat deposition is unusual the patients tending to be on the lean and muscular side However female or eunuchoid fatty depositions are occasionally encountered

Nothing is known with certainty as to aetiology but genetic or chromosomal factors are probably fundamental This view is supported by the occasional occurrence of pseudo hermaphroditism in siblings The adrenal cortex is said to be enlarged in 14 per cent of pseudo hermaphrodites but hyperplasia and hyperfunction without anatomical enlargement is more frequent and in ovarian pseudo hermaphrodites almost appears to be more immediately aetiological It certainly explains the enlarged clitoris the undeveloped ovaries and the hirsutism all of which may be produced by injecting pregnant animals with androgens It has also been pointed out (see Hermaphroditism) that oestrogens will similarly produce hypospadias

In previous papers on the adrenogenital syndrome and feminization in the male (Simpson et al 1936 Simpson and Joll 1938) it has been shown that the adrenal cortex (neoplasm or hyperplasia) secretes a relative and absolute excess of oestrogens in the male and of androgens in the female (see Adrenal section) This so far as it goes may explain the mechanism although not the initial cause of both testicular and ovarian pseudo hermaphroditism Biological urinary assay in pseudo hermaphroditism is as yet incomplete but pathological hyperactivity of the adrenal cortex is suggested by high androgen high oestrogen or high pregnanediol assays in some patients (Genitis and Bronstein 1942)

Histologically it is the glomerular and fascicular layers of the adrenal cortex that are usually hypertrophic and not the inner reticularis layer although the last named is said to be comparable to the androgenic or X zone of mice

In some infant pseudo hermaphrodites enormously enlarged adrenal glands (cortex) without haemorrhage are found at autopsy after severe vomiting and collapse of unknown origin (Dijkhuizen and Behr 1940) A similar clinical and pathological condition is found in infants with normal genital development (Skelton 1945)

(i) Testicular Pseudo hermaphroditism

External Genitals

The penis may be small or of normal size but it is frequently held down to the perineum by congenital fibrous bands and the resulting concave bending of the penis towards the perineum (chordee) tends to prevent erection and make the organ less prominent When it is small it is often mistaken for a large clitoris Hypospadias is nearly always present and the urethra may open under the glans at the base of the penis or several centimetres behind in the perineum or in the vestibule between pseudo labial folds as in the female The scrotum is bifid and where the two halves fail to meet a vaginal or pseudo vaginal orifice presents itself with a varying degree of labia formation This opening may have no depths or may have the dimensions and histological structure of a true vagina According to the relative size of the penis (or assumed clitoris) and degree of failure of union of the scrotal folds (pseudo or real vagina) the child is brought up initially as a girl or as a boy

Testes

The testes are usually undescended but if the scrotal folds are well developed the testes may have partially descended and be palpable Their macroscopic appearance is usually testicular and they may be normal in size or small Microscopically they show apparently normal interstitial cells but although the seminiferous tubules are frequently well formed spermatogenesis is not found Sterility is the rule even when coitus and seminal emissions are possible

Uterus and Fallopian Tubes

In some testicular pseudo hermaphrodites there are no female organs apart from a pseudo vagina but in others there may be found usually in a hernial sac an infantile uterus and Fallopian

tubes In one such case the gonad was in the position in which the ovary is usually found and its consistency and appearance were ovarian in character but subsequent section showed it to be a testis

Urination

Owing to the hypospadias especially when the urethral opening is perineal or vestibular most patients complain that they are unable to urinate except in the sitting position as assumed by the female

Hair

The pubic hair is abundant and may be either of the female type limited horizontally in its upper boundary or of the male triangular type extending to the umbilicus Rarely however is much hair present on the body The facial hair is of male type but usually scarce and slow growing so that shaving is not a daily procedure This would appear to indicate that in spite of normal interstitial cell tissue the secretion of androgens is subnormal or alternatively there is low responsiveness of the hair follicles or a scarcity in their distribution on the face The probability of a subnormal intensity of androgenic stimulus is supported by the fact that the prostate is usually subnormal in size

Breasts

The breasts are usually flat and of male type but they have responded to oestrogen therapy when such has been attempted

Somatic Development

The general habitus is that of male type with shoulders broader than the pelvis Muscular development however may be poor and is rarely excessive Tall thin eunuchoid types as well as adipose eunuchoid types have also been recorded but are not the rule

Libido and Sexual Behaviour

This depends to some extent on whether the patient is assumed to be a boy or a girl in childhood but even so the predominant type of behaviour appears to be masculine Thus

after freeing the penis from adhesions to the perineum satisfactory vaginal penetration and coitus with orgasm and emission are usual and happy married life achieved The fluid emission comes from urethral and prostatic glands and contains no spermatozoa Masturbation is frequent with younger patients and in adults if coitus is not possible

Some patients have been brought up as girls perhaps in convents and then on the finding of testicular tissue in the gonads have adopted with success male clothing and habits Others have had the clitoris removed and both before and more so after enlargement of the vagina have married their male lovers and lived sexually and socially as women although both gonads were testes and no uterus or Fallopian tubes were present

Diagnosis

Diagnosis is uncertain until both gonads have been inspected and biopsy material examined histologically

Treatment

This consists of freeing the penis from adhesions plastic operation on the hypospadias and closure of the vaginal orifice In some patients the external genital structure and the psychological attitude justifies removal of the penis and enlargement of the vagina

(ii) Ovarian Pseudo hermaphroditism

Genitals

The external genitals may not differ from those of the testicular pseudo hermaphrodite The clitoris is considerably enlarged and resembles a penis and the phallus may be used successfully as a penis in intercourse with females The clitoris has a glans and a section of its body may show corpora spongiosa and cavernosa as in the male The urethra opens at its base or in the perineum or vestibule The labia majora may be (1) completely fused giving the appearance of a bifid scrotum or (2) incompletely fused with a minute vaginal orifice or (3) well formed with underlying labia minora surrounding a normal vaginal opening and hymen

When no vaginal orifice is present a urethroscope will reveal a vaginal orifice opening into the urethra Such a vagina may

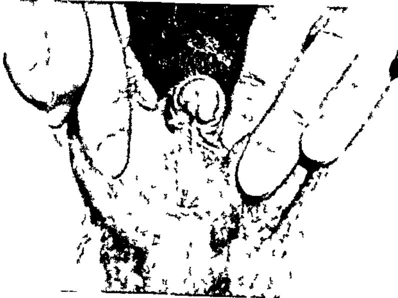


Fig 7 Ovarian Pseudo hermaphroditism This patient was referred to me by Dr Ursula Shelley Was brought up as a girl until the age of 3 The growth of the clitoris deepening of the voice and growth of pubic hair caused the parents to regard him then as a boy and has been brought up as such (now aged 13) in spite of the fact that at the age of 5 a laparotomy showed a uterus two ovaries and Fallopian tubes there was also considerable enlargement of the right suprarenal gland Growth stopped at the age of 9 when facial hair appeared Second picture shows vagina and clitoris resembling small penis Patient is therefore an ovarian pseudo hermaphrodite

be of considerable size and depth and the cervix of the uterus may be visualized The injection of iodized oil through a catheter will show the shape and size of the vagina on a radiographic picture taken subsequently A male type of prostate is some times present around the urethra and may be palpable per rectum

Ovaries and Uterus

The ovaries are usually intra abdominal and are found on laparotomy They are usually infantile or in an adult may be found to correspond to normal ovaries of a child of 10 years of age They may however be involuted and fibrotic with multiple cysts Normal adult ovaries with well developed Graafian follicles and corpora lutea are not usually found In fact the ovaries are similar to those found in cases of adrenogenital syndrome or experimentally when a female animal is injected with testosterone It is probable that the failure of development of the ovaries is due to the androgens secreted by hyperplastic adrenals The uterus and Fallopian tubes are also poorly developed in the majority of patients Amenorrhoea is the rule but slight bleeding or vaginal discharge or vicarious nasal menstruation are met with

Urination

This is carried out as by the normal female but in some patients incontinence of urine or urgency of micturition is met with The vagina may open into the urethra or the urethra may open into the vestibule as in the normal female and inter mediate positions of the urethra on the perineum are sometimes found

Hair

Some patients have a feminine distribution of hair and none on the face but the majority have a male distribution of hair and may have a moustache and beard This too is attributable to androgens secreted by hyperplastic adrenals Hair on the face may be present in childhood but may not develop until puberty This would indicate either that the ovaries then secrete androgens or that the adrenals take on increased activity at puberty The latter seems more probable

Breasts

The breasts are usually flat and of male type Sometimes they appear more feminine in structure

Somatic Development

In childhood as in cases of sexual precocity due to an adrenal tumour development is precocious and a child of 4 may have the muscular and skeletal development of a child of 8 or 10 This was so in one of my patients and the voice was deep The bone age and epiphyseal development is advanced The relative proportion of shoulders to pelvis is usually of male type but a gynaecoid pelvis may be encountered

Libido and Sexual Behaviour

One of my patients was brought up as a girl to the age of 3 when a deepening of the voice some hair on the face a more noticeable enlargement of the clitoris (phallus) and boyish attitudes caused an assumption of male sex At the age of 13 when he appeared to be a 4 foot sturdy little man with a moustache of two years standing laparotomy revealed a uterus and ovaries

In the majority of patients the libido is inclined towards males even when the patient is hirsute and the clitoris enormous If the vagina is patent or made patent sexual intercourse with the male is usually satisfactory Rarely the adult hermaphrodite may function as a male in coitus with a female

Diagnosis

Diagnosis is uncertain until both gonads have been inspected and biopsy material examined histologically

Treatment

Amputation of the clitoris and plastic enlargement of the vagina is usually advisable Young retains the glans portion of the clitoris if possible as it is a sensitive erotic zone Where the libido is of male type, and the vagina rudimentary reconstruction of a large phallus is justifiable together with closure of the vagina if the urethral orifice can be dealt with by plastic surgery The advantage of this approach is the solution of the hirsutism

problem Where the patient leads a female life as is general the facial hair presents the same problem as in the adrenogenital syndrome Young performs partial bilateral adrenalectomy with variable results

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CHAPTER XLI

ABNORMALITIES OF MENSTRUATION

MENORRHAGIA metrorrhagia or amenorrhoea may be part of obvious clinical disorders of the endocrine glands (e g adreno genital syndrome hyperthyroidism myxoedema) and as such are considered elsewhere in the present work This chapter deals with such abnormalities of menstruation as appear to be the principal if not the only manifestations of endocrine disorder The cause is usually primarily pituitary secondarily ovarian but this aetiology though based on sound theoretical grounds often remains unproved Local abnormalities such as carcinoma fibroids polypi chronic endometritis and salpingitis are excluded from discussion but the onus of asking a gynaecologist to exclude such abnormalities is on the physician prescribing endocrine therapy Enlargement of the uterus and even polyposis of its endometrium may however be manifestations of excessive follicular activity (ovarian) The physician must also be on the look out for general disorders which affect menstruation such as tuberculosis and anaemia

Menorrhagia

Definition

In the absence of gross gynaecological abnormalities menorrhagia may be due to a deficiency or absence of progesterone secretion as is indicated by a proliferative and not a secretory pre menstrual endothelium (biopsy) and the absence of pregnanediol from pre menstrual urine In normal women pregnanediol is excreted in variable amounts ranging from 3 to 60 mg per day in the progestational phase of the menstrual cycle (Scowen 1944) Its absence suggests the absence of ovulation and of corpus luteum formation

Treatment

The logical treatment of such patients is the giving of progesterone e g 10 mg injected every other day in the second half of the cycle the dose being reduced after some months Alternatively I have implanted 400 mg of progesterone in the

subcutaneous fat of the abdomen under local anaesthesia Unfortunately progesterone tablets tend to extrude themselves to a far greater extent than tablets of any other hormone Apart from this progesterone by either method is effective only in a proportion of such patients possibly 60 per cent All types of gonadotrophic preparations have been used but results are on the whole poor

Testosterone by injection e g 25 mg three times a week or by implantation (400 mg) is effective in controlling menorrhagia but has the disadvantage of producing acne deep voice and some hirsutism It acts by inhibiting the pituitary secretion of gonadotrophic hormone and menorrhagia returns if therapy is stopped Prolactin has been used with success and theoretically this may be due to its luteotrophic action (Hall Kupperman and others 1944) Karnaky (1940) and McCann (1942) have both found that massive doses of stilboestrol will stop menorrhagia presumably by pituitary inhibition and that normal menstruation may follow its cessation My own experience is more variable Where the basal metabolism is low thyroid therapy is indicted

All hormone therapy may fail Repeated curettage often fails Resection of apparently normal or polycystic ovaries unless complete may fail In intractable cases hysterectomy may be the only effective procedure although this admission may indicate our comparative ignorance of gynaecological endocrinology

Amenorrhoea

Definition

Absence of menstruation for long intervals of months or years is termed amenorrhoea (absence of menstruation) It is said to be primary when the patient has never menstruated or secondary if it supervenes after some years of normal menstruation Oligomenorrhoea is the term applied to scanty menstruation

Clinical

Amenorrhoea may be present as part of a major endocrinopathy e g adrenogenital syndrome Cushing s syndrome infantilism acromegaly thyrotoxicosis Simmonds s disease &c It may occur with non endocrine disorders e g anorexia nervosa or any psycho neurosis or psychosis or with severe debilitating illness

or avitaminosis Apart from these conditions primary amenorrhoea is comparatively rare and is due to specific failure of the pituitary gonadotrophic stimulus This is also true of many cases of secondary amenorrhoea The latter may however be due to excess of follicle stimulating hormone and lack of luteinizing hormone Polycystic ovaries may be associated with amenorrhoea

Treatment

Gonadotrophic stimulation fails in primary amenorrhoea It may succeed in secondary amenorrhoea if massive doses of follicle stimulating hormone are given for 2 weeks followed by luteinizing hormone in the next 2 weeks and the cycle repeated e g 3 000 units monthly of F S H and L H An alternative therapy is with Synapoidin a preparation containing pituitary gland gonadotrophins and chorionic gonadotrophins

Substitution therapy may be tried in both primary and secondary amenorrhoea It consists of a total of 50 mg of oestradiol benzoate or stilboestrol for 2 weeks followed by a total of 50 mg progesterone in the next 2 weeks Zondek found that good results could be obtained with progesterone only the assumption being that some oestradiol is secreted endogenously Where cystic ovaries are present bilateral subtotal resection is indicated

Metropathia Haemorrhagica

This term is usually applied to a condition of severe uterine haemorrhages occurring at completely irregular intervals and often with intermittent phases of prolonged amenorrhoea It appears to be due to excess of pituitary follicle stimulating hormone and absence of luteinizing hormone Scowen (1944) found a complete absence of pregnanediol in the urine The ovaries may show several enlarged Graafian follicles without corpora lutea or polycystic ovaries The uterine endometrium is usually of a proliferative hyperplastic type

The condition may be refractory to all hormone therapy and Stein (1945) advocates subtotal wedge resection of both ovaries Adequate treatment with progesterone in large doses may however control the condition and even be followed by spontaneous normal menstruation Scowen advocates 20 mg of progesterone

injected on alternate days for four doses and then a gradual reduction of this dosage until the patient is maintained on as little as 10 mg per month The initial treatment is followed by a menstruation of normal duration and intensity It is of interest that pregnanediol does not appear in the urine until a week or more after initiating treatment This suggests an initial starvation of the tissues for progesterone comparable to that found for vitamin C in deficiency states Anhydro hydroxy progesterone (ethisterone) by mouth is inferior to progesterone by injection in controlling haemorrhages

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CHAPTER XLII

PREGNANCY

PREGNANCY should not be thought of as a condition affecting only the reproductive glands and organs even when it is entirely physiological and uncomplicated by disease Through the inter relationship of the endocrine glands changes are probably produced in all the endocrine glands the effects being only temporary in many cases but in others a residual degree of change persists The extent of this physiological change depends on what I have termed the endocrine constitution of the individual The reality of such an endocrine constitution can be appreciated by observing familial endocrine tendencies or stigmata as variants of so called normality and more specifically by studying for example the effects of bilateral ovariectomy Some women will gain 3 stones in 6 months after bilateral ovariectomy while others will not change weight some will have almost unbearable vasomotor and nervous symptoms others will have none Similarly with pregnancy some women show minimal endocrine changes others put on weight during pregnancy and/or after each successive pregnancy while others develop or increase pre existing hirsutism temporarily or permanently These are normal changes probably associated with the hypertrophy of the anterior pituitary gland and adrenal cortex which we know occur in experimental animals during pregnancy There is an indefinite dividing line between such normal physiological changes and the development of morbid conditions

Hormone Tests for Pregnancy

The Ascheim-Zondek (mice) and Friedman (rabbit) tests for pregnancy are well known and commonly used the former taking 5 days and the latter from 24 to 48 hours A 6 hour test on rats has recently been evolved by Salmon and colleagues (1942) All tests depend upon the high concentration of chorionic gonadotrophic hormone in pregnancy urine and its effect on the ovary

Ascheim–Zondek test Six infantile mice are used each weighing from 6 to 8 gm A first morning specimen of urine is collected acidified slightly with dilute acetic acid and 0 25 c c are injected

subcutaneously twice daily for three successive days No injections are given on the 4th day and the mice are killed on the 5th day If the test is positive the ovaries examined by a hand lens will show several corpora lutea or punctate haemorrhages A morning specimen of urine contains a higher concentration of hormone than one collected during the day Some six mice are used since one or more may die before the test is completed and occasionally one is unresponsive to the gonadotrophic stimulus The accuracy of the test is 99 per cent There are on record however definite pregnancies that gave more than one completely negative reaction More than 60 per cent of pregnancies will give a positive result when the patient is only 2 days over due and more than 90 per cent when the patient is 10 days overdue The appearance of a positive test depends upon the nidation of the ovum and the establishment of a metabolic interchange between the trophoblast and the maternal circulation The test remains positive throughout pregnancy up to about the tenth day post partum A positive test does not mean that the foetus has remained alive It only means that the trophoblast has remained alive and the placenta may go on living several months after the foetus has died If a positive test subsequently gives place to a negative test this indicates the death of the foetus but such a test should be repeated and taken in conjunction with the clinical findings The test will be positive in an ectopic gestation as long as there is a living chorionic epithelium intra abdominal rupture and haemorrhage are considered unlikely in the presence of a persistently negative test Both hydatid mole and chorion epithelioma usually give a positive Ascheim–Zondel and the concentrations of gonadotrophic hormone is ten times as high as in normal pregnancy but a mole may be present with a negative test The test may remain positive 6 weeks after the expulsion of a hydatid mole but if it persists longer than this or if it becomes positive again after having been negative a chorio epithelioma should be suspected

Friedman test Rabbits do not ovulate spontaneously but only on coitus or pseudo coitus or if gonadotrophic hormone is injected Immature female rabbits of 12 weeks are used and kept in separate cages for 2 or more weeks Then 10 c c of morning urine are slowly injected into the ear vein of the rabbit and laparotomy or killing is carried out 24 or 48 hours later the

CHAPTER XLII

PREGNANCY

PREGNANCY should not be thought of as a condition affecting only the reproductive glands and organs even when it is entirely physiological and uncomplicated by disease Through the inter relationship of the endocrine glands changes are probably pro duced in all the endocrine glands the effects being only temporary in many cases but in others a residual degree of change persists The extent of this physiological change depends on what I have termed the endocrine constitution of the individual The reality of such an endocrine constitution can be appreciated by ob serving familial endocrine tendencies or stigmata as variants of so called normality and more specifically by studying for example the effects of bilateral ovariectomy Some women will gain 3 stones in 6 months after bilateral ovariectomy while others will not change weight some will have almost unbear able vasomotor and nervous symptoms others will have none Similarly with pregnancy some women show minimal endocrine changes others put on weight during pregnancy and/or after each successive pregnancy while others develop or increase pre existing hirsutism temporarily or permanently These are normal changes probably associated with the hypertrophy of the anterior pituitary gland and adrenal cortex which we know occur in experimental animals during pregnancy There is an indefinite dividing line between such normal physiological changes and the development of morbid conditions

Hormone Tests for Pregnancy

The Ascheim-Zondek (mice) and Friedman (rabbit) tests for pregnancy are well known and commonly used the former taking 5 days and the latter from 24 to 48 hours A 6 hour test on rats has recently been evolved by Salmon and colleagues (1942) All tests depend upon the high concentration of chorionic gonado trophic hormone in pregnancy urine and its effect on the ovary

Ascheim-Zondek test Six infantile mice are used each weigh ing from 6 to 8 gm A first morning specimen of urine is collected acidified slightly with dilute acetic acid and 0 25 c c are injected

various stages of pregnancy and parturition for a variety of reasons He found that there was an absence of reactivity in the earliest stages followed by a greater reactivity to vasopressin than oxytocin and then in the later stages a gradual increase in the reactivity to oxytocin culminating in labour So that the inherent reactivity of the uterus at various phases of pregnancy is as important as the circulating hormones unless one assumes that the circulating hormones have produced some change in the uterine muscle which determines its response to oxytocin even after excision In a further paper Robson (1933) points out that the reactivity of the uterus after parturition falls rapidly although the luteal secretion must by then have practically ceased He points out that oestrin which is secreted by the placenta as well as by the ovary has a progressively increasing high concentration in the blood during pregnancy reaching a maximum at parturition and rapidly decreasing after expulsion of the placenta and that the concentration of oestrin determines the reactivity of the uterus to oxytocin This thesis was proved experimentally by Robson and others in later experiments on animals Falls Lackner and Krohn (1936) claimed to prove by an intra uterine pressure bag that in the human uterus oestradiol increased and progesterone decreased the sensitivity of the human uterus to an oxytocin stimulus They also showed that progesterone was effective in counteracting a threatened abor tion or a tendency to abortion that could be anticipated from the experience of previous pregnancies These and subsequent papers by others have met with criticism and some scepticism Davis Hamblen Cuyler and Baptist (1942) have produced some biological data and clinical studies which tend to confirm older theories They showed that initial low levels of or fall in urinary values for sodium pregnanediol glucoronide were asso ciated with abortion and that progesterone was effective in the prophylaxis and treatment of threatened abortion They in jected 5 to 20 mg of progesterone daily or twice weekly but found that anhydrohydroxy progesterone given orally in daily doses varying from 20 to 60 mg was equally effective Falls and others (1942) also found progesterone effective in threatened abortion and in cases of surgical emergency necessitating laparotomy in which the prevention of onset of labour or abor tion was desired

later period of time being more reliable One or more haemorrhagic follicles are positive of pregnancy The test is correct in 90 per cent of cases or more but when in doubt an Ascheim-Zondek test should also be carried out

Salmon test This test is of recent origin and has the advantage of giving a result within 6 hours Three immature rats (weight 35 to 45 gm aged 22–5 days) are injected subcutaneously with 2 c c of the night specimen of urine and autopsied at the end of 6 hours If the test is positive the ovaries are enlarged and bright red in appearance in sharp contrast to the small white or faintly pink ovaries of the control animals This test was positive in 77 out of 78 pregnancy urine tests and negative in 31 out of 31 non pregnancy urines See also F Sulman et al (1945)

Xenopus test This test first described by Hogben in 1939 is popular in South Africa where the toad *Xenopus laevis* on which the test is performed breeds naturally Those who have used the test consider it reliable The mechanism is the same as that of the Ascheim–Zondek and Friedman tests namely the production of ovulation by chorionic gonadotrophins of pregnancy urine 1 c c of a prepared extract is injected intraperitoneally or in the dorsal lymph sac A positive test shows within 6 to 24 hours engorgement of the cloacal labial (cloacal reaction) or more convincingly the extrusion of many eggs visible on the bottom of the jar as small spheres These toads have been imported and bred in London and New York and successfully used for pregnancy testing

Parturition and Abortion

In 1929 Knaus showed that the human uterus does not react to pituitrin (containing both oxytocin and vasopressin) during the second part of the menstrual cycle when the corpus luteum is active and it has been generally held that progesterone tends to inhibit uterine contraction and that a fall in the level of progesterone may initiate parturition or abortion Bilateral ovariectomy however does not necessarily interfere with pregnancy or parturition in the human subject and Robson and Illingsworth (1932) were unable to demonstrate any progestational or inhibitory hormone in the four placentas removed at various stages during gestation Robson (1933) studied the reactivity of the uterus to oxytocin and vasopressin removed at

intermedia and often an infiltration of the pars nervosa by basophil cells The significance of these findings is also disputed (Lennox 1942) Mukherjee (1941) returned to the biological approach and showed that filtrates from the blood of toxaemic women contained a melanophore expanding principle an anti diuretic substance and a vasopressor substance the relative proportion of the latter two constituents corresponding to the clinical picture

Hain (1940) found that in normal women in the last 3 weeks of gestation a marked increase in the excretion of oestrogens and pregnanediol took place and in pre eclampsia or eclampsia the values for both were higher than in normal women and especially high were the pregnanediol values In one patient a sudden marked rise in pregnanediol followed intra uterine death The complexity of the subject however is shown by the observations of Smith and Smith (1941) who found that the earliest and most constant sign in pre eclampsia and eclampsia was the elevation of serum gonadotrophins (implying a placental abnormality) and that there is a progressive deficiency of progestin a con comitant decrease of oestrogen and a consequent changed metabolism of oestrogen involving greater and more rapid de struction Shute (1940) also found that the blood of eclamptic women revealed low oestrogen values and records observa tion on the treatment of ten true pre eclamptics and six con vulsive eclamptics to show the beneficial effects of oestrogens in the treatment of these cases He also warns against the giving of vitamin E to eclamptic women since this produces a still further lowering of the blood oestrogen values and records that one of the writer s patients developed a fulminating toxaemia ending in convulsions when large doses of wheat germ oil had been administered without the precaution of a pre liminary test of blood oestrogen level —and that a colleague had two similar experiences He adds that there is a large gap in the chain of evidence As to treatment he gave 50 000 inter national units of oestradiol subcutaneously and repeated this within 24 hours if no benefit In some cases spontaneous labour supervened Cohen Marrian and Watson (1935) point out that normally during the greater part of pregnancy over 99 per cent of the total oestrogenic material excreted in the urine is in the combined ether soluble form which possesses only a low

The opposite effect of inducing abortion by large doses of oestradiol has been attempted and is generally considered ineffective at least in the early stages of pregnancy Large doses of oestradiol (Jeffcoate 1937) or of stilboestrol (Peel 1939) have been used with more success for inducing abortion after the intra uterine death of the foetus or in the treatment of uterine inertia In the latter condition Jeffcoate used in one case 20 000 units of oestradiol spread over 12 hours in another case 1 300 000 units spread over 5 days in a third 800 000 units spread over 12 hours and in a fourth 700 000 units spread over 12 hours Reynolds (1939) reviews work published on the use of oestradiol in pregnancy He concludes that it has not been proved of value in attempting to induce abortion with a live foetus or inducing premature labour It does however appear to be of value in uterine inertia and he quotes with approval the work of Jeffcoate and colleagues and its most promising use appears to be in cases of intra uterine death including missed abortion as in such cases the dead foetus may be retained in the uterus for a considerable time if oestradiol is not employed This is also important in so far as the usual oxytocics are without effect in missed abortion and if effective are not free from danger

Pregnancy Toxaemia and Eclampsia

An excellent review of the essential literature is to be found in the *British Medical Journal* (1942) Hofbauer (1918) first *postulated an endocrine basis for eclampsia and Kustner (1928)* demonstrated that the blood of an eclamptic woman contained a substance which would stimulate expansion of melanophores in the frog In 1932 Anselmino Hoffman and Kennedy drew attention to the fact that chronic pituitrin poisoning in rabbits produced pathological changes in the kidneys resembling those seen in pregnancy toxaemia They also claimed to have demonstrated that during toxaemia there occurs an increased production of posterior pituitary hormones vasopressin and antidiuretic and that as the clinical severity of the toxaemia increases so can greater concentration of these hormones be demonstrated in the blood These findings have led to much controversy and some contradiction Cushing (1933) approached the problem from a histological angle and showed that in fatal cases of eclampsia there was a basophilic hyperplasia of the pars

latter alveolar growth However both fail to act in a hypophysectomized animal whereas pituitary extracts produce breast development the essential constituent being named Mammogen It is therefore postulated by Selye and Collip (1936) that ovarian hormones act on the mammary gland indirectly by way of their pituitary stimulating effect Mammogen is concerned with breast development but another pituitary hormone prolactin is responsible for the initiation of lactation Its secretion during pregnancy is prevented by the concentration of oestrogens in the blood but when these fall at parturition prolactin is secreted and lactation begins Should the pituitary mechanism not respond lactation will not commence or will be inadequate In such cases (but not in all cases of poor lactation) prolactin (e g Physolactin) may be injected intramuscularly 5 c c 5 c c 2 c c 2 c c and 1 c c on successive days and lactation may thereby be induced or improved Its maintenance depends upon the suckling reflex When a child is still born it is necessary to suppress lactation and this can be done by oestrogens or androgens both inhibiting pituitary secretion Fifty thousand units of oestradiol or 5 mg of stilboestrol or hexoestrol may be injected 12 hourly or 24 hourly the dose being progressively reduced by each injection over a period of a few days or 50 mg androgens repeated daily for a few days is equally effective

Diabetes Mellitus

This disorder should not be diagnosed unless the reducing substance in the urine is known to be glucose (not lactose) and the tolerance curve is a characteristic diabetic one Renal glycosuria or diabetes innocens associated with normal blood sugar values and a low renal threshold for glucose may occur during pregnancy and is of no significance Diabetes mellitus may start during pregnancy and if slight may disappear after pregnancy to recur at a successive pregnancy or to become permanent later on It seems probable that diabetes mellitus arising in pregnancy may be of pituitary origin and due to the pituitary hyperplasia that occurs in pregnancy and ultimately may become a pancreatic diabetes as in the experimental pituitary diabetes of dogs (Young 1939 Best and others 1939) It is therefore essential to treat even mild diabetes in pregnancy with care and thoroughness because in this way a permanent

physiological potency It is therefore no longer difficult to reconcile the production of large amounts of oestrogenic substances in the body during the pregnancy with the fact that the injection of oestrin into pregnant animals may interfere with the normal course of gestation

It seems to the writer that a great deal of the abnormal hormone findings in eclampsia may be due to a diseased placenta as this hormone is the source of oestrin progesterone and gonadotrophin but that excess of vasopressin from a hypertrophied pituitary may produce vaso spastic changes and resulting infarction in the placenta On the whole one is tempted to agree with the cynical view that eclampsia is a disease of theories

Pernicious Vomiting of Pregnancy

Anker and Laland (1938) found high serum values and low urinary values of anterior pituitary like principles in patients with pregnancy vomiting as compared with uncomplicated pregnancy Freeman and Melick (1935) found that extract of the suprarenal cortex was of value in pernicious vomiting of pregnancy but put forward no theoretical consideration Many remedies however have been advocated for vomiting of pregnancy In the early stages of pregnancy the commonest cause is psychological but in the later stages of pregnancy pernicious vomiting is probably a manifestation of toxaemia of pregnancy Anselmino (1936) states that with pernicious vomiting of pregnancy there is a disturbance of carbohydrate metabolism an inability to store glycogen and an increase in ketone bodies due to an increase in fat metabolism He also observes that there is an absence of hypertrophy of the adrenal cortex in hyperemesis gravidum as compared with that which occurs in normal pregnancy If this be so it would constitute a rationale for therapy with adrenal cortical extracts Synthetic desoxycorticosterone however should not be used as it tends to produce salt and water retention Corticosterone the carbohydrate regulating factor in cortical extracts is not available commercially as a pure synthetic preparation

Lactation

Oestrogens and progesterone both influence mammary development the former stimulating duct development and the

foetal death rate in diabetes mellitus They carried out assays of chorionic gonadotrophin and pregnanediol in the urine of 125 diabetic women after the 24th week of pregnancy In 41 women these hormones were present in normal concentration and 95 per cent of foetuses survived In the remaining 84 cases there was an increased excretion of gonadotrophin and decreased excretion of pregnanediol Twenty seven of these abnormal patients were untreated by hormones and 60 per cent of the foetuses survived Fifty patients with abnormal hormone excretion were treated by large doses of progesterone and stilboestrol in the latter half or third of pregnancy and the foetal survival rate was as high as 92 per cent The authors also record that toxaemia appeared to be modified by this hormone therapy If this work is confirmed it would appear to call for the routine assay of chorionic gonadotrophin and pregnanediol in pregnant diabetic women as the apparent effect of appropriate hormone therapy on foetal death rate is striking

As to whether diabetics should have children from a eugenic point of view the answer is in the negative if there is a family history of diabetes in both parents and an indecisive answer if only on one side of the family Otherwise the answer is Yes if the mother desires children and is intelligent The Mendelian recessive theory is not universally accepted

Diabetes Insipidus

This is a rare complication of pregnancy and when it appears in pregnancy often disappears after parturition A pre existing diabetes insipidus may be aggravated ameliorated or uninfluenced by pregnancy (Blotner and Kunkel 1942) The condition is readily controlled by injections of pitressin tannate in oil

Thyrotoxicosis

This condition may have its onset in pregnancy probably due to a pituitary thyrotrophic stimulus in a patient with a constitutional thyroid sensitivity More commonly pregnancy may supervene in a thyrotoxic patient although with severe degrees of thyrotoxicosis pregnancy is unlikely and if it occurs may be followed by spontaneous abortion The treatment of pregnancy in a severely thyrotoxic patient used to be abortion in the early months and this may be justifiable If however a child is

diabetes may be prevented just as diet or insulin may prevent experimental pituitary extract diabetes becoming permanent pancreatic diabetes

Pregnancy does occur in diabetics especially if well controlled by diet and insulin although the fertility rate is lower than normal When pregnancy does occur the danger is greater to the foetus than to the mother The causes of the high foetal mortality rate (some 40 per cent) are due mainly to the large size of the foetus and to an increased incidence of toxaemias among diabetics (Smith Smith Joslin and White 1937) while *other causes are post natal hypoglycaemia and perhaps a slightly* increased incidence of congenital defects Maternal mortality has fallen from 45 to 2 per cent since the introduction of insulin The insulin requirement is normally raised during the second *half of pregnancy and falls again rapidly after delivery when* great care must be taken to avoid insulin hypoglycaemia The ultimate requirements of insulin are not necessarily greater than before pregnancy In diabetic women as with normal women the renal threshold is frequently lowered in pregnancy so that blood sugar estimations are necessary as well as urine testing The renal threshold is not a static level and tends to its lowest level about the fifth month of pregnancy

As regards foetal size in 45 instances Lawrence and Oakley (1942) found that 27 babies weighed above 9 lb and 13 of these weighed between 10 and 12 lb Caesarean section was performed in 27 cases between the 36th and 38th week and 23 of the babies survived 19 births were spontaneous and 11 babies survived 3 were induced and 2 survived The total foetal mortality was 33 per cent They conclude that pregnancy should always be terminated at the 36th to the 38th week and favour Caesarean section in primipara and induction in multipara This is in keeping with Joslin s experience To avoid the possibility of insulin hypoglycaemia in the new born baby (owing possibly to compensatory islet cell hypertrophy) glucose should be given 2 hourly during the first 48 hours although Joslin records that in the last 25 babies in his clinic this has not been necessary Lactation is often deficient in a diabetic but breast feeding should be attempted whenever possible

Priscilla White and Hazel Hunt working at Joslin s Clinic have recently made an interesting contribution to the study of

persist This is due to the physiological hypertrophy of the anterior pituitary gland overstepping normality in an individual with constitutional acromegaloid tendency If pregnancy supervenes in an acromegalic woman it should be allowed to run its normal course unless there is clinical evidence of severe aggravation of the acromegaly Lactation may be excessive and prolonged in acromegaly after weaning of the baby but can be checked by oestradiol or testosterone (See Lactation)

Cushing's Syndrome

This is a condition described by Cushing in 1932 and characterized by hirsutism amenorrhoea adiposity plethora hypertension *glycosuria and rarefaction of bones &c and is associated* with a basophil adenoma of the anterior pituitary gland and/or hyalinization of the (remaining) basophil cells and/or neoplasm or hyperplasia of the adrenal cortex Cushing pointed out that the disease not infrequently commenced during pregnancy Cohen (1937) has described a case in which the syndrome appeared during pernicious vomiting of pregnancy and progressed to extreme degree Spontaneous abortion was followed by a complete remission and the whole process was repeated in the next pregnancy when a further abortion led to another remission This striking case lends support to the view that adiposity and mild hirsutism that not infrequently occur in pregnancy with partial or complete remission after parturition are manifestations of pituitary and adrenal gland changes beyond the physiological concomitants of pregnancy The so called pregnancy cells of the anterior pituitary gland are believed by Rasmussen to be eosinophil in origin but it seems probable from the above considerations that the basophil cells are also increased and all cellular elements of the anterior pituitary may be involved in pregnancy hyperplasia their proportion or extent varying with the underlying endocrine constitution of the patient

Simmonds s Cachexia

This disorder is not really a complication of pregnancy except in so far as its cause may be due to something that happens at parturition The condition was originally described by a Hamburg pathologist in a fatal case of puerperal fever at the autopsy of which atrophy of the anterior lobe of the pituitary was found

desired an early thyroidectomy is indicated and is likely to result both in the cure of the thyrotoxicosis and a successful pregnancy The recent discovery of the beneficial effects of thiouracil in thyrotoxicosis will permit the continuation of pregnancy under medical supervision or in combination with irradiation of the thyroid gland If the thyrotoxicosis is not severe iodine and sedatives may permit a successful pregnancy and the thyrotoxicosis may improve in the middle trimester

Addison's Disease

This condition due to deficiency of the suprarenal glands may have its onset in pregnancy or pregnancy may supervene in a typical case of pre existing Addison s disease In the latter case the adrenal insufficiency will be aggravated but adequate treatment with cortical extract and desoxycorticosterone may permit a pregnancy to be continued successfully to full term The risk to the mother however is considerable and unless there are very good reasons for attempting a difficult task abortion should be performed in the first 3 months Some patients with Addison s disease have a history of minor mani festation of the disorder in a previous pregnancy with disap pearance of the symptoms after parturition and onset of the disease proper some years later In others the disease com menced in pregnancy and continued subsequently In both cases the adrenal glands were probably affected in slight degree by tuberculosis or idiopathic atrophy before pregnancy super vened and the manifestation of the adrenal insufficiency was brought about because of the extra demands made upon the adrenal cortex during pregnancy It is probable that the pig mentation seen in some women during pregnancy is a manifesta tion of temporary adrenal insufficiency as may be other features e g gastro intestinal disorders asthenia and low blood pressure and treatment with adrenal cortical extract has appeared to be of benefit in such circumstances

Among the author s patients with Addison s disease several have had successful single pregnancies and one has had two live babies (Simpson 1946)

Acromegaly

Mild acromegaly may occur in pregnancy and may tend to

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secondary to an arterial embolus Sheehan and Murdoch (1938) point out that necrosis of a portion of the anterior lobe occurred more frequently than was realized as a result of thrombosis or embolus when parturition is associated with severe haemorrhage or infection and that the syndrome may be incomplete and chronic The classical features of Simmonds s cachexia are amenorrhoea loss of secondary sexual characteristics subnormal temperature and metabolism loss of weight and bradycardia I have recently seen a patient who developed the incomplete syndrome following a pregnancy at the age of 32 in the year 1918 She had several attacks of severe and prolonged spontaneous hypoglycaemic coma which responded to intravenous glucose but the last attack (1943) was fatal and at autopsy there was atrophy of the anterior pituitary and of the adrenal cortex (secondary to the pituitary) Thus the condition may be chronic over a period of 25 years I have seen another case following parturition which had been treated as myxoedema for many years with a very incomplete response to thyroid gland as might be expected (Simpson 1947) Thus care and skill at parturition and in the pre natal supervision may prevent the onset of a very severe disorder which may prove fatal at once or within a few months or many years later or that may lead to chronic invalidism Whether adequate and immediate blood transfusions would prevent thrombosis of the pituitary vessels following a severe parturition haemorrhage it is difficult to know but it is a problem that calls for consideration and this might be preferable to awaiting a slower recovery from severe bleeding There is much to be said in favour of immediate blood transfusion

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of the Graafian follicles (F S H) and Prolan B causes ovulation and corpus luteum formation (L H) In the Physiological section we have seen that this is not true of the mammal and some clinicians have reported negative results Others have said the injections must be given intramuscularly Rydberg and Pedersen Bjergaard (1943) investigating by means of urinary assays of oestrone and pregnanediol excretion laparotomies and endometrial studies found that true ovulation and sometimes pregnancy could be induced by the following technique of treatment Prolan A (e g Serogan or Gestyl) 3 000 international units on the fourth and ninth day of the menstrual cycle followed by Prolan B (e g Pregnyl or Antuitrin S) 1 500 units every other day for three injections all injections being given by the intramuscular route Although some patients with anovular menstruation do ovulate after this and similar techniques the absence of consistent results does raise the question of *post* or *propter*

With all gonadotrophic preparations and especially if the intravenous route is used severe allergic reactions may be encountered

Genital hypoplasia and idiopathic sterility sometimes respond to the giving of oestrogens in the first half of the cycle and progesterone in the second half e g a total of 25 mg of oestradiol injected or 50 mg stilboestrol by mouth followed by a total of 50 mg progesterone by injection

MALE STERILITY

Definition

The term is usually applied to a male who can perform coitus normally but the examination of whose seminal fluid reveals an absence of spermatozoa or a severe diminution in their number together with pathological changes in their morphology motility and resistance to environment or chemicals In my opinion a mere reduction in numbers without pathological changes is not sufficient to diagnose sterility

Causes

Mumps complicated by orchitis and gonorrhoea complicated by epididymo orchitis are perhaps the best recognized causes However in my opinion infection of any kind including

CHAPTER XLIII

STERILITY

IN THE FEMALE

Definition

An absence of fertility when the male partner has normal seminal fluid

Clinical

Sterility may be part of a general endocrinopathy e g adreno genital syndrome Cushing s syndrome or one manifestation of amenorrhoea Such forms however are considered under their respective headings Sterility may be due to non endocrine causes e g occlusion of the Fallopian tubes (often gonococcal in origin) tuberculous endometritis usually without other symptoms and said to constitute 5 per cent of all cases of idiopathic sterility In this section we will consider only three forms

(1) anovular menstruation
(2) genital hypoplasia
(3) idiopathic sterility

Diagnosis

It is assumed that a gynaecologist has excluded non endocrine causes Anovular menstruation may be diagnosed by pre menstrual biopsy of the uterine endometrium which shows a proliferative endothelium and not a secretory one (see Physio logical section)

Genital hypoplasia may be diagnosed clinically by the finding of an infantile uterus presumably due to inadequate ovarian activity secondary to an inadequate gonadotrophic stimulus The hypoplasia may apply also to the Fallopian tubes and be of such a degree that these tubes have not become patent

Treatment

Anovular menstruation has been treated by the injection of large doses of Prolan A (pregnant mare s serum) in the first half of the menstrual cycle and large doses of Prolan B (pregnant women s urine) in the second half Prolan A stimulates growth

Lumbar sympathectomy should not interfere with ejaculation or fertility—presacral sympathectomy does. Prostatectomy usually results in sterility but not impotency. A urogenital surgeon should examine sterile patients to see if there is any blockage in the duct system from the testis to the urethra although it is rarely possible to take any satisfactory surgical steps for cure

Biopsy of the testis is a simple procedure and will reveal whether the seminiferous tubules are destroyed beyond power of regeneration

Treatment

In my experience the treatment of male sterility is very disappointing. Logical therapy is the injection of pituitary or pregnant mare's serum gonadotrophins which theoretically could stimulate the seminiferous tubules if biopsy indicates that they are capable of responding. Small and large doses of testosterone have been advocated on the basis that the seminiferous tubules depend upon testosterone for their proper functioning but no conclusive results have been published

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influenza may harm the seminiferous tubules without any clinical evidence of orchitis at the time Syphilis is a rare cause

Clinical

It is increasingly recognized that childless marriages may be due to male sterility as well as to female sterility and some writers find the former to be the cause in 30 per cent of cases Certainly examination of the seminal fluid should never be omitted in the absence of gross pathology of the female

Male sterility is completely compatible with full virility normal primary and secondary sexual characteristics strong libido *and full capacity for frequent coitus* All these things depend upon the secretion of androgens by the interstitial cells of Leydig The quantity and quality of the seminal fluid depends upon the structure and function of the seminiferous tubules These are much more sensitive to noxious stimuli than are the interstitial cells

Diagnosis

This depends upon examination of the seminal fluid This should be collected directly into a porcelain dish as a masturbatory *specimen and examined immediately or into a glass* tube with a waxed cork which is kept at room temperature and delivered to the doctor within 3 hours Rubber condoms destroy motility and I have seen many patients who have been wrongly *informed* that sterility was due to their spermatozoa *being dead or not* viable when this method of collection had been used Seminal fluid may also be obtained from the woman's cervix after coitus

The number of spermatozoa are counted by a simple technique of *examination in a* white cell chamber after suitable dilution with saline formalin The normal number is given as 60 to 100 million per c c and the average quantity of seminal fluid as 4 to 6 c c In my experience counts above 10 million are quite compatible with fertility Counts should not be made within 3 days of coitus or within a fortnight of influenza or other infections Slides are made and stained and the morphology of the spermatozoa studied *For details readers are referred to* papers on *technique* (Harvey and Jackson 1945 *Charney and* Meranze 1942)

potence relative or absolute among the civilian population This too was usually psychogenic It should be recognized however that long hours of work and excessive physical fatigue combined with some exacerbation of the normal worries of everyday life produce impotence If this is misunderstood by the wife as rejection or dealt with unsympathetically especially as a reflection on manhood it is likely to lead to permanent impotence the man being unwilling to risk depreciatory or scornful comments on an inadequate performance

Psychogenic impotence is entirely uninfluenced by testosterone therapy and this is an expression of a general law which I would formulate namely that psychogenic inhibition prevents the normal response of tissues or organs to hormones whether secreted by the patient s own glands or given by injection in concentrations many times the normal

Organic This may be met with as primary hypogonadism or as part of a major endocrine syndrome There is associated absence of libido or masturbatory activity or nocturnal emissions A response to testosterone therapy is usual but not invariable An absence or diminution of secondary sexual characteristics is not infrequent but the genitals may or may not be infantile

Types of Organic Impotence

(1) Eunuchoidism (q v)
(2) Infantilism (q v)
(3) Frohlich s syndrome (q v)
(4) Destruction or removal of anterior lobe e g craniopharyngioma chromophobe adenoma
(5) Cushing s syndrome (q v)
(6) Feminization due to adrenal tumour (q v)
(7) Diabetes mellitus In this condition impotence is not as rare as is generally believed The cause is not obvious except in diabetes due to haemochromatosis when the anterior pituitary and/or the testicle may be infiltrated and destroyed by haemosiderin In ordinary diabetes mellitus impotence may supervene after some years even when the treatment has been reasonably efficient It does not always respond to testosterone Possibly one group of cases is due to hyperplasia of the adrenal cortex

CHAPTER XLIV

IMPOTENCE

Definition

The term is applied to males only and may be defined as inability to perform or complete coitus

Clinical

The main differentiation is between psychological and organic impotence

Psychological In psychological impotence the primary and secondary sexual characteristics are apparently normal and there is no obvious endocrinopathy present It is always or nearly always part of a general psycho neurotic clinical picture Every endocrinologist is faced with a large number of these patients who believe that there is something wrong with their testicles or glands

If the patient states directly or on questioning that he experiences erections and emissions spontaneous or masturbatory quite apart from any attempts at coitus the impotence is of psychological origin Premature ejaculations on attempting coitus are also psychogenic If strong erections are followed by premature tumescence without emissions the disorder is psychological Weak or transitory erections are often psychogenic

A very high incidence of impotence sometimes as much as 80 per cent was found among returned prisoners of war even when there was no evidence of vitamin deficiency The coexisting masturbatory activities or nocturnal emissions suggested its psychogenic origin In some patients coitus had been normal when in prisoner of war camps and had been possible by various temporary escapes and subterfuges but impotence occurred on returning to home life in England After a period of adjustment potency returned At an Army Conference on the subject at which I was present as consulting endocrinologist it was agreed that in 90 per cent or more of the prisoners of war complaining of impotency the condition was part of a neurosis and should be treated as such

During and after the war there was also a good deal of im

CHAPTER XLV

HOMOSEXUALITY

Definition

This term is usually applied to men and the corresponding condition in women is called Lesbianism Both conditions may be defined as sexual gratification with a person of the same sex although the term sexual should be considered in its broadest aspect including cultural and aesthetic Although the observations below refer to male homosexuality they are applicable to Lesbianism Homosexuals tend to play a passive (feminine) or active (masculine) role but may act in both roles

General Observations

Homosexuality in tendency if not in expression is normal for a phase of life—boyhood and adolescence—just as auto sexuality is normal in infancy and early childhood Nevertheless homosexuality expressed genitally is not universal at this phase although this form is more widespread than is generally realized

If homosexuality persists in adult life when heterosexuality is the more normal expression of libido it can be considered pathological Its cause is an arrest of normal evolution of the individual and the causes are (1) genetic and (2) psychogenic (environmental) Even in those homosexuals who have effeminate physical characteristics there is no evidence of an endocrine disturbance and it is more likely to be a genetically determined behaviour pattern although one cannot exclude an associated genetic disposition or disturbance of the endocrine glands

Androgen assays have not shown any significant difference in value between homosexuals and normals Glass and colleagues (1940) found that the androgen–oestrogen ratios in homosexuals were lower than those observed in normal males Kinsey (1941) was unable to confirm these observations

Treatment

As an endocrinologist I would state as my experience that testosterone or any other endocrine therapy is valueless in an attempt to convert a homosexual to a normal heterosexual

which produces both the diabetes and testicular inhibition

(8) Severe infections and extreme vitamin deficiencies

Diagnosis

The presence of other endocrine features indicates organic impotence and neurotic symptoms favour the diagnosis of psychogenic impotence Masturbatory or homosexual activities indicate psychogenic impotence Response to testosterone therapy confirms the diagnosis of organic impotence and excludes the diagnosis of psychological impotence *The reverse of this statement is only partially true In psychological impotence if masturbatory activity occurs the semen may show normal* seminal fluid with millions of active well formed spermatozoa

The 17 ketosteroids may be within normal limits in both psychological and organic impotence but a high normal value suggests psychogenic impotence and a low value organic impotence

Treatment

In organic impotence one treats the general condition and where there is primary or secondary hypogonadism testosterone *is indicated Its dosage and form is the same as is described under Eunuchoidism*

With psychological impotence the treatment is psycho therapeutic Sometimes a few relatively superficial talks and reassurance are sufficient In others prolonged psycho analysis may be required and may ultimately fail

CHAPTER XLVI

PROSTATE

THERE is no evidence that the prostate is an endocrine gland secreting a hormone It is however dependent upon hormones secreted by other glands for its proper functioning and pathological changes may be induced by these hormones Castration in the male rat is followed by atrophy of the prostate and a return to normal is produced by testosterone Testosterone in the intact animal will also produce hypertrophy of the prostate compared with normal control animals Oestrogens have the same effect on the prostate as castration in male rats but act by physiological inhibition of secretion of the pituitary gonadotrophic hormone with resulting involution or atrophy of the testes Oestrogens in female rats will produce enlargement fibrosis and metaplasia of the prostate homologue and this action can be prevented by testosterone The application of these basic facts to clinical malignant and benign enlargement of the prostate is considered below

Over 150 years ago John Hunter pointed out that the prostate owes its activity to the existence of the testicles and that their removal caused atrophy of the gland Further complete orchidectomy for the relief of prostatic cancer was practised by many of the older surgeons although the operation fell into disuse probably because of the lack of any ultimate benefit and the psychological repugnance that the idea produced However there has been a revival of this procedure Thus Nesbit and Cummings (1942) reported on 75 cases of carcinoma of the prostate treated by orchidectomy and observed for periods of at least 6 months Although no cures were claimed favourable subjective and objective responses were obtained in no less than 73 per cent of cases In a follow up of these series (1944) they reported Forty five per cent of the patients remain free from symptoms 21 to 36 months after orchidectomy but 21 patients previously reported as showing favourable response have had recurrent symptoms of advanced disease and several of these are dead The increasing incidence of delayed failure in this series suggests that eventually all cases may fall into this

Surgical castration has been advocated, but its results are quite unpredictable and passive homosexuality might well be anticipated. The same objection might be raised to physiological castration by stilboestrol, but here at least the effects are reversible and in the control of the physician.

The psychiatric approach to homosexuality is logical and some cures result. There are, however, a large proportion of complete failures or relapses. The problem remains a social one and the good of the individual may conflict with the welfare of the community. The State is beginning to approach the problem with greater understanding, but its task remains a difficult one.

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review by Professor Dodds of this field of cancer research it is important to record that he stated no single member of the workers in this field has ever claimed a cure It is true that clinical regression and a stationary condition of well being has been observed for 2 years but nothing under 5 years can be considered as adequate evidence even of permanent regression when dealing with carcinoma of the prostate

Disadvantages of the therapy are enlarged painful breasts (gynaecomastia) disappearance of libido and potency a diminution in size of the penis and testicles and sometimes oedema of the ankles and lower limbs All these and in addition hot flushes occur with castration therapy One patient treated with oestradiol dipropionate developed a purpuric syndrome which was controlled by 1 gm of calcium gluconate by mouth t d s Huggins in his original papers pointed out that the enzyme phosphatase is apparently secreted by the epithelial cells of the prostate (normal values up to 3 5 units per 100 c c serum) that it is considerably increased in carcinoma of the prostate (usually above 10 units) and that stilboestrol therapy as well as castration will produce a return to normal levels the estimation of serum acid phosphatase thus affording a method of controlling dosage and progress Radiation of the testes (radiation castration) has often been advocated as an alternative method for the control of carcinoma of the prostate Experimentally it is easy to destroy the spermatic tubules by radiation but not the interstitial cells which secrete testosterone Huggins found that radiation of the testes was inadequate as a therapeutic agent in prostate cancer in man He also observed that if there was an unsatisfactory response to surgical castration the addition of stilboestrol therapy was of no avail This seems to confirm the view that stilboestrol acts by producing physiological castration and not by direct action On the ground that androgens are secreted by the adrenal cortex as well as by the testes both adrenal glands have been removed where relapse had followed castration for prostatic cancer and where the relapse had been associated with a return of the 17 ketosteroids in the urine from the post castration low levels to more normal levels Although bilateral adrenalectomy reduced the 17 ketosteroids per litre of urine from 12 mg to 1 mg there was no clinical amelioration and autopsy showed that the malignant prostatic growth was

category Kretschmer (1943) reports a disappointing series of cases and judged by the strict criteria usually applied to alleged remedies for cancer finds orchidectomy a disappointing procedure except for transitory amelioration in some patients Other papers have appeared including those of Huggins and colleagues (1941) and Lane (1943) and the evidence tends to show that temporary amelioration occurs in 50 per cent of patients as evidenced by improvement in general health and well being improvement in the consistency and mobility of the prostate decrease in dysuria and striking and rapid relief from pain due to secondary growth in the bones &c

In view of the above preliminary physiological considerations it was eminently rational to substitute stilboestrol (or other oestrogen) therapy for surgical castration in an attempt to ameliorate the clinical condition associated with carcinoma of the prostate but if this is the only action of stilboestrol it would not be justified to expect results of greater value than those obtained with surgical castration The numerous clinical reports suggest on the whole a similar character to those obtained with surgical castration although some workers in this field have made more optimistic claims even over long periods Initial work with oestrogens in carcinoma of the prostate is usually attributed to Huggins and Hodges (1941) but in a letter to the *Journal of the American Medical Association* Herbst (1944) points out that in a previous month he read a paper on the subject to the American Urological Association and a summary of his results appeared in the *Journal of the American Medical Association* in 1942 Several other papers appeared in America (Huggins 1942 Huggins and colleagues 1941 and Herrold 1941) and in this country (Fergusson 1944 Walker 1943 Dodds 1944 and Duncan 1944) There is general agreement among most observers The dose of stilboestrol is 3 mg daily for some 2 months and then reduction to 1 mg daily is usual Some two thirds of the patients respond and benefit is shown by diminution or disappearance of pain on micturition and pain associated with bony metastases decrease of frequency decrease in size and fixity of the prostatic gland increase in weight and well being decrease in size of bone pulmonary and spinal metastases and occasional disappearance of superficial subcutaneous metastases In view of a misquoted

SECTION SIX

THE PANCREAS

A PHYSIOLOGY

CHAPTER XLVII

INTRODUCTION

UNTIL a decade or so ago a discussion of the physiology of carbohydrate metabolism would centre around the classical experiments of pancreatectomy by Mering and Minkowski (1889) and the discovery of insulin by Banting and Best (1921) and its mode of action The fundamental character of these observations and experiments will always remain but to day the field of thought must be widened by a recognition of the very important part played physiologically and pathologically by the pituitary and adrenal glands

INSULIN

Paul Langerhans described islets or small clumps of epithelial cells in the pancreas in 1869 Mering and Minkowski (1889) showed that excision of the pancreas resulted in glycosuria diabetes and death and that these sequences could be prevented by a small pancreatic graft and finally Banting and Best (1921) succeeded after many had failed in extracting insulin from the pancreas The final chemical stages of their work were brought to fruition by the brilliant chemical collaboration of Collip whose work in the field of hormone chemistry is outstanding Insulin had been obtained from the pancreas by Zuelzer in 1908 and it is not known whether the then fatal results following its use in man which put an end to this work were due to a toxic chemical impurity or failure to recognize the fatal hypoglycaemia of overdosage Banting and Best working in Macleod s laboratory in Toronto proceeded on the theory that trypsin destroyed the secretion of the islets of Langerhans They therefore ligatured the pancreatic duct to produce atrophy of the acini the islets remaining intact or appearing to undergo hypertrophy Later it was shown that such a preliminary procedure is quite unnecessary

still active (Huggins and Scott 1945) It has been observed that testosterone administration increases the serum acid phosphatase as well as aggravating the symptoms in prostatic cancer In general one can conclude that it has been proved possible to mitigate the symptoms and prolong life and well being in patients with carcinoma of the prostate but as yet cure' cannot be claimed

The theoretical aspect of the relation between prostatic enlargement the testes and stilboestrol is further complicated by the fact that benign enlargement of the prostate has been treated both by testosterone and by stilboestrol and good results claimed The writer was a member of a Committee of the Medical Research Council which organized extensive clinical trials and controls and was unable to consider as proved the claim that testosterone was of real value in benign enlargement of the prostate Nevertheless many clinicians continue its use on the theory that the prostate becomes enlarged in old age as testicular function fails and because they obtain symptomatic improvement Stilboestrol is used on similar theories as those considered above for carcinoma of the prostate and in a recent paper Skibba and Irwin (1944) claim good results

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of the positive reactions to pancreatectomy namely hyperglycaemia increased break down of body protein and production of ketones We shall see later that this response of the liver to deprivation of insulin is brought about through the anterior pituitary lobe

Insulin is said to have the following main functions

(1) The transference of sugar from the peripheral blood to the peripheral tissues This is indicated by the increased difference between the level of arterial and venous blood (A–V difference) on the injection of insulin

(2) The combustion of glucose by the tissues This was indicated by the apparent inability of the pancreatectomized animal to burn glucose the respiratory quotient remaining low e g 0 7 unless insulin were given with the glucose when it rose to 1 0 (Lusk 1928) Himsworth (1938) pointed out a possible fallacy to this argument namely that fat could be changed into carbohydrate in the depancreatized animal which in itself would lower the respiratory quotient The peripheral utilization of sugar in the depancreatectomized animal is shown by the fall of blood sugar after hepatectomy Himsworth concluded that the power to combust carbohydrates is impaired rather than lost in the absence of insulin

(3) The stimulation of the formation of glycogen by the muscles and in some circumstances by the liver Insulin will only increase the glycogen content of the liver if there is a plentiful supply of carbohydrate Otherwise it might decrease it because of the mobilization of glycogen to compensate for hypoglycaemia The formation of glycogen by the liver is more specifically a function of the adrenal cortex (which see) and less directly of the anterior pituitary Insulin retards glucogenesis from glycogen since it abolishes the necessity for a high level of blood glucose to permit glucose utilization

(4) Inhibition of glucose formation from amino acids In a starving diabetic or in depancreatized animals the glucose in the urine is derived from a break down of tissue protein as is *indicated by the constant dextrose nitrogen D N ratio of 3 6* About 60 per cent of injected protein is converted into glucose Insulin will inhibit this break down of protein

(5) The conversion of carbohydrate into fat This has been suggested by Lawrence (1946) as an important normal function

That the islets secrete insulin is indicated by the above experiments by their degeneration in some patients with diabetes mellitus by their degeneration in experimental diabetes (e g dogs) produced by pituitary diabetogenic hormone by their hypertrophy after partial pancreatectomy and by hyperinsulinism associated with islet cell tumours The islets contain two kinds of cells distinguishable by the character of their granules, which can be demonstrated by intra vitam staining with neutral red α granules are fixed in alcoholic solution while the β granules are fixed in watery solution The β granules are seen in the above experiments to be responsible for insulin secretion and when lesions are present in the pancreas in human diabetes it is the β cells which show degeneration The name insulin according to Rolleston (1936) was suggested by de Meyer in 1909 and independently by Schafer in 1916

The Action of Insulin

The action of insulin cannot be understood without a preliminary consideration of the function of the liver in carbohydrate metabolism The work of Mann and Magath (1922) on hepatectomized dogs showed what a fundamental part the liver plays in the stabilization of the blood sugar level Their dogs died in hypoglycaemic convulsions within a few hours of the *removal of the liver Continuous intravenous injections of* dextrose could prevent this for a while although death from hepatic failure followed within 30 hours The muscles of the hepatectomized animals contained glycogen which apparently could not be used in the absence of the liver to provide glucose The normal process is the conversion of muscle glycogen to lactic acid then to hepatic glycogen and then to glucose (Corri 1931) If pancreatectomy is performed at the same time as hepatectomy the rate of fall of blood sugar is less suggesting a peripheral action *of insulin Further insulin increases the rate of* fall of blood sugar after hepatectomy

In the experimental production of diabetes by pancreatectomy in addition to hyperglycaemia there is an excessive breakdown of body protein as indicated by urinary nitrogen and of fat as indicated by ketonuria Removal of the liver from the depancreatized dog leads to a fall of blood sugar of urinary nitrogen and of ketonuria Thus the liver is the seat

trophic glycotropic and diabetogenic factors (or hormones) play in carbohydrate metabolism will be considered later The glucose tolerance of the hypophysectomized animal or of the human subject with destruction of the anterior pituitary gland has appeared to vary under different conditions of observation Soskin (1938) pointed out that this depends upon the route of administration of glucose and the method of calculation Since hypophysectomy retards the intestinal absorption of glucose the latter should be given intravenously when testing carbohydrate tolerance Since the initial and final blood sugar values are lower in the hypophysectomized animal than in the control animal the tolerance curve gives the impression of increased tolerance if however the percentage increases of blood sugar values are plotted the tolerance appears decreased if absolute values are plotted and the whole curve displaced upwards so that the initial blood sugar values are superimposed upon those of control normal animals the curves are identical However hypersensitivity to injected insulin and the retarded recovery of blood glucose after the initial depression are constant and characteristic findings in hypophysectomized animals

Soskin has also shown that the Staub–Traugott effect is not obtained in the absence of the anterior pituitary Normally if a carbohydrate tolerance curve is repeated and then again repeated at short intervals the curve gets lower and lower This Staub–Traugott effect does not occur in hypophysectomized animals and in fact the tolerance actually decreases Soskin attributes the Staub–Traugott effect to a progressive depression in the activity of the pituitary gland

PANCREATROPHIC OR INSULOTROPHIC FACTOR

Hypophysectomy does not cause apparent degeneration or decrease in the number of islets of Langerhans (and in fact a paradoxical increase has been recorded see Griffiths 1941) Nevertheless Anselmino Herold and Hoffman (1933) found that the injection of extracts of anterior pituitary into normal rats induced an increase in the number and size of the islets of Langerhans Although this histological work has not been fully confirmed Marks and Young (1939) observed that the insulin content of the rat pancreas could be increased some 200 per cent by such extracts The islets in the remaining portion of

of insulin and in the absence of the ability of the organism to store fat (lipodystrophy—which see) hyperglycaemia and lipaemia develop

The Character of Insulin

Insulin is a protein like substance of high molecular weight which has been isolated in pure crystalline form but the exact composition of which is not yet known It is soluble in water and relatively stable in acid solutions It is destroyed by pepsin and trypsin

POSTERIOR PITUITARY

The effect of posterior pituitary extract in raising the blood sugar on injection has been known for nearly 40 years (Bachardt 1908) and the antagonism between insulin and posterior pituitary extract was demonstrated by Burn in 1923 He found that the fall of blood sugar in rabbits after insulin was counteracted by large doses of posterior pituitary extracts Several investigators subsequently confirmed this and found that vasopressin and pitocin (oxytocin) were equally effective The blood sugar raising effect of pituitrin did not occur if the liver was empty of glycogen but in addition to this glycogenolytic effect the A–V increase produced by insulin was partially inhibited suggesting that pituitrin interfered with the peripheral action of insulin Pituitrin does not counteract insulin if the latter is given intravenously This may be due to the fact that pituitrin delays the absorption of subcutaneous insulin or that greater doses are required to counteract intravenous insulin the qualitative effect of pituitrin being so small compared with insulin Wislicki (1943) found that pitressin but not oxytocin (pitocin) was the anti insulin factor but that pituitrin was greater in activity than equivalent amounts of pitressin and oxytocin injected together

ANTERIOR PITUITARY

The very large part played by the anterior pituitary gland in carbohydrate metabolism is obtaining increasing recognition and the chemists are differentiating several factors The low blood sugar low glycogen content of the liver and hypersensitivity to insulin of the hypophysectomized animal have been known for some time What part the pituitary pancrea

pituitary will correct all the metabolic abnormalities indicated above

The Houssay animal is one in which both the anterior pituitary gland and the pancreas have been removed The symptoms of pancreatic diabetes are considerably alleviated if hypophysectomy is carried out at the same time or before or afterwards Survival is prolonged though not indefinitely Glycosuria is less and the blood sugar varies between 0 1 and 0 25 per cent Sometimes spontaneous hypoglycaemic crises occur There is also a hypersensitivity to insulin The ketones in the blood and urine are much less than after pancreatectomy and the alkali reserve is normal or only slightly diminished The catabolism of proteins is only slight and the dextrose–nitrogen ratio is low The lipoids and cholesterol in the blood rise less than in the controls The hepatic and muscular glycogen may be found in normal or only slightly sub normal quantities If sugar is given the R Q rises (although not as much as in normal animals) showing that sugar can be burnt even in the absence of the pancreas Houssay concludes that in pancreatic diabetes the secretion of the anterior pituitary increases the production of glucose and diminishes its consumption

If anterior pituitary extracts are injected into Houssay animals (hypophysectomized depancreatized) the mild diabetes is considerably aggravated in every way Houssay found that bilateral adrenalectomy did not prevent this diabetogenic action of pituitary extracts but that hepatectomy did These findings were also true for otherwise normal animals injected with such pituitary extracts the effects of the latter being recorded by Houssay as hyperglycaemia glycosuria a high glucose nitrogen ratio in the urine hyperlipaemia hypercholesterolaemia ketosis diabetic type of glucose tolerance curve and failure of the R Q to rise on the giving of glucose Houssay concluded that the diabetogenic action of the pituitary gland (or extracts) is independent of the adrenals The demonstration of the diabetogenic action of pituitary extracts in normal animals was also shown by Evans Meyer Simpson and Reichert (1932) and by Baumann and Marine (1932) The glycogen stores of animals made diabetic by pituitary extracts are not lowered

The production of diabetes in the dog by daily injections of equal amounts of pituitary extracts can be divided into three

the partially excised pancreas of a rat undergo hyperplasia (Friedman and Marble 1941) as was originally contemplated by Allen in 1913 and it is probable that this is attained by secretion of the pituitary pancreatrophic hormone Conn and Louis (1944) have produced further confirmatory evidence in man by showing that pituitary extracts exacerbate the low blood sugar and produce hypoglycaemic crises in patients with pancreatic islet tumours and organic hyperinsulinism The e extracts were diabetogenic in dogs as were the pituitary extracts which were pancreatrophic in rats For this reason the response appears to depend upon the species of test animal and it is by no means certain that the pancreatrophic and diabetogenic factors are different chemical factors Nevertheless biologically speaking there is good evidence of a pituitary factor which in certain species under certain circumstances is pancreatrophic and insulotrophic

DIABETOGENIC FACTOR

Nearly all the earlier fundamental work on the diabetogenic action of the anterior pituitary gland was carried out (1924–37 &c) in a pioneer manner by Bernardo Houssay Professor of *Physiology in the Faculty of Medical Science at the University* of Buenos Aires in the Argentine and his colleague and pupils F G Young (1936 1938) working under the auspices of the Medical Research Council of Great Britain carried this work a vital step forward when he produced permanent diabetes in dogs by progressively augmenting doses of an anterior pituitary extract with resulting degeneration of the islets of Langerhans

Houssay working initially with toads showed that the anterior pituitary gland and not the posterior was the fundamental part of the gland responsible for diabetogenic action In hypophysectomized animals (toads dogs rabbits &c) there is a rapid fall of blood sugar on fasting and hypoglycaemic convulsions hypersensitivity to the action of insulin low hepatic glycogen (if fasting) a normal or slightly diminished muscle glycogen and an increased carbohydrate tolerance (There is no inability to burn glucose since the R Q is normal and rises on glucose administration as in the normal animal) Implanted anterior pituitary gland or the injection of extracts of anterior

the action of which is overshadowed in some species e g dogs by the diabetogenic action whereas in others e g rats the pancreatrophic factor has such a powerful response that the diabetogenic action can never be demonstrated

GLYCOTROPIC FACTOR

Cope and Marks (1934) showed that certain pituitary extracts injected into rabbits could prevent the hypoglycaemic action of insulin without however their having the power to raise the blood sugar when injected alone Young (1937) introduced the name glycotropic factor to separate this function from the diabetogenic complex of which it may be a part since the initial action of the latter may be manifested by a decreased sensitivity to insulin (see above) and nothing else This glycotropic factor appears to attach itself to the prolactin factor but can be separated from it as well as from the thyrotrophic and gonadotrophic factors Himsworth and Scott (1938) showed that neither the thyroid nor the hypophysis nor the adrenal glands are necessary in rabbits for the action of the glycotropic factor in antagonizing the action of insulin

Cope and Marks (1934) obtained results which led them to suggest that the glycotropic factor rendered the liver glycogen less stable so that the depression of blood sugar by insulin was rapidly countered by outpourings of glucose from the liver This corresponded to their finding that after hypophysectomy the liver glycogen is abnormally resistant to mobilization However Young (1938) found that the hyperglycaemic action of injected adrenaline (by glucogenesis from hepatic glycogen) is the same whether or not glycotropic substance is also injected if the adrenaline is given intravenously (although it is rendered greater by glycotropic substance if adrenaline is injected subcutaneously) He concludes that the glycotropic substance apparently does not antagonize the hypoglycaemic action of insulin by facilitating the glycogenolytic action in the liver of adrenaline secreted by the adrenal glands It may directly antagonize the action of insulin both in the liver and in the peripheral tissues

Marks (1936) showed that the glycotropic factor injected into decapitated eviscerated cats injected with glucose and insulin diminished the peripheral removal of glucose from the blood and the rate of deposition of muscle glycogen Himsworth and

phases (Young 1937 1938) (1) a latent phase of 3-5 days during which glycosuria or ketonuria is not observed and the blood sugar level is little affected, and during which period the animal develops a relative resistance to the hypoglycaemic action of injected insulin (2) the phase of temporary diabetes lasting for 3-7 days during which glycosuria ketonuria and polyuria appear rise to maximum values and then decline and disappear despite the continued daily injection of the same amount of extract the animal remaining relatively insensitive to the hypoglycaemic action of insulin during this phase and the liver glycogen being normal or raised and (3) the refractory phase lasting for weeks or months in which the animal is unresponsive to daily injections of pituitary extracts

Young s great contribution (1937) at this stage of our knowledge was to show that this refractoriness could be overcome by using large and increasing doses of pituitary extracts and further that a permanent diabetes was induced by this method and persisted indefinitely after all injections were stopped The cause of this permanent diabetes was a degeneration of the β cells of the islets of Langerhans the α cells being unchanged By studying the islets of pancreatic glands at various stages of the experiments Young and Richardson (1938) found (a) mitosis and proliferation (b) hydropic degeneration (c) disappearance of granules and (d) hyalinization It is suggested that the proliferation precedes the degeneration

Marks and Young (1940) investigated the metabolism of dogs thus made permanently diabetic The insulin requirements were greater than those of depancreatized dogs in spite of this such dogs are able to survive much longer without insulin treatment than depancreatized dogs the D N ratio was high 3 1 and the sugar tolerance curve of a strongly diabetic type There is evidence that anterior pituitary extracts result in increased production and mobilization of carbohydrate and inhibition of the peripheral utilization of glucose The reaction of the islets of Langerhans is secondary to this and their subsequent failure to meet the situation is manifested by this degeneration

Extracts of pituitary gland which are diabetogenic in dogs have no such action in rats where a pancreatrophic action only is demonstrable This suggests that the diabetogenic complex of pituitary gland extracts contains also a pancreatrophic factor

the action of which is overshadowed in some species e g dogs by the diabetogenic action whereas in others e g rats the pancreatrophic factor has such a powerful response that the diabetogenic action can never be demonstrated

GLYCOTROPIC FACTOR

Cope and Marks (1934) showed that certain pituitary extracts injected into rabbits could prevent the hypoglycaemic action of insulin without however their having the power to raise the blood sugar when injected alone Young (1937) introduced the name glycotropic factor to separate this function from the diabetogenic complex of which it may be a part since the initial action of the latter may be manifested by a decreased sensitivity to insulin (see above) and nothing else This glyco tropic factor appears to attach itself to the prolactin factor but can be separated from it as well as from the thyrotrophic and gonadotrophic factors Himsworth and Scott (1938) showed that neither the thyroid nor the hypophysis nor the adrenal glands are necessary in rabbits for the action of the glyco tropic factor in antagonizing the action of insulin

Cope and Marks (1934) obtained results which led them to suggest that the glycotropic factor rendered the liver glycogen less stable so that the depression of blood sugar by insulin was rapidly countered by outpourings of glucose from the liver This corresponded to their finding that after hypophysectomy the liver glycogen is abnormally resistant to mobilization However Young (1938) found that the hyperglycaemic action of injected adrenaline (by glucogenesis from hepatic glycogen) is the same whether or not glycotropic substance is also injected if the adrenaline is given intravenously (although it is rendered greater by glycotropic substance if adrenaline is injected subcutane ously) He concludes that the glycotropic substance apparently does not antagonize the hypoglycaemic action of insulin by facilitating the glycogenolytic action in the liver of adrenaline secreted by the adrenal glands It may directly antagonize the action of insulin both in the liver and in the peripheral tissues

Marks (1936) showed that the glycotropic factor injected into decapitated eviscerated cats injected with glucose and insulin diminished the peripheral removal of glucose from the blood and the rate of deposition of muscle glycogen Himsworth and

Scott (1938) found confirmatory evidence of this in rabbits in which the liver had been removed from the circulation since the pituitary glycotropic factor inhibited the action of insulin in accelerating the removal of blood glucose by the peripheral tissue although it did not affect the rate at which these tissues use glucose spontaneously However in rabbits in which the liver was only partially excluded the animals which had received the glycotropic factor reacted to a fall in blood sugar (after insulin) by an excessive liberation of sugar from the liver into the blood

The term glycotropic is not a happy one The first half of the word refers to glucose and not to glycogen and the word should therefore be glucotropic Tropic means a turning towards Glycotrophic is sometimes used instead trophic' meaning nourishing and is an even less satisfactory term Young has expressed to me his own dissatisfaction with the term he initially proposed and he now prefers simply anti insulin factor

(The term glycostatic has been applied by Russell and Bennett (1936) to a factor of the pituitary extract which prevents the abnormal depletion of muscle glycogen in hypophysectomized animals which is said to be due to an abnormally high rate of carbohydrate oxidation in the muscles In this case glycostatic means tending to keep glycogen stores stationary The term is not to be confused with glycotropic)

THE PITUITARY KETOGENIC FACTOR

We have seen in previous sections that pituitary diabetogenic extracts can produce ketosis as part of the diabetic picture but such ketosis can result without diabetes Burn and Ling (1930) first showed that an extract of pituitary injected into fat fed rats produced an increased excretion of ketones At the same time there is a rapid accumulation of fat in the liver at the expense of the fat depots (Best and Campbell 1938) Ketonaemia also has been produced by injecting pituitary extract (Anselmino and Hoffmann 1933) and this work has been repeatedly confirmed Ketogenic effects cannot be obtained in the absence of the liver (Mirsky 1936) Although ketones can be formed to a slight extent from certain amino acids or pyruvic acid for all practical purposes they are an index of the cata

bolism of fat The theory of β oxidation is now replaced or modified by the MacKay theory of β oxidationacetic acid condensation hypothesis (Soskin and Levine 1941)

Although anterior pituitary extracts will cause a rise in the ketone bodies of the blood in the normal animal in which adequate amounts of insulin are being secreted for all ordinary purposes yet the administration of extra insulin diminishes or abolishes such ketosis (Houssay 1936 Mirsky 1936) Further in the depancreatized animals the hyperlipaemia and fatty infiltration of the liver are both inhibited by insulin Blixen krone Moller (1938) found that pituitary extracts can cause hyperlipaemia by liberation of fat from fat depots The effect of the adrenal cortex on ketosis is considered separately (see Adrenal section)

For many years it has been held that the ultimate oxidation of ketone bodies was dependent upon the simultaneous oxida tion of carbohydrates the idea being expressed in the classical phrase fats are burnt in the furnace of the carbohydrate It has been shown by perfusing the muscles of both normal and diabetic eviscerated dogs that ketone bodies are completely combusted to CO_2 and water in the muscles independently of any carbohydrate oxidation (Snapper and Gruenbaum 1928 Chaikoff and Soskin 1928) Ketonaemia is therefore a measure of excessive ketone formation by the liver which occurs in the absence of an adequate carbohydrate substance for energy requirements The peripheral oxidation of the considerable excess of ketone bodies fails quantitatively but not qualitatively

THE ADRENALS AND CARBOHYDRATE METABOLISM

The liberation of adrenaline from the adrenal medulla and its conversion of hepatic glycogen to glucose as an emergency measure is well known The adrenal cortex however plays a much more important part in carbohydrate metabolism and the specific hormones belong to the group of steroids oxygenated at C 11 e g corticosterone 11 dehydro corticosterone and 11 dehydro 17 hydroxy corticosterone The mode of action has been discussed in the Adrenal section In summary these hormones are diabetogenic removal of the adrenal cortex ameliorates pancreatectomy diabetes the adrenal cortex is responsible for the change of lactic acid (derived from muscle

carbohydrate diet depressed the sensitivity to insulin Insulin sensitivity is measured by the rate at which blood glucose is lowered after a standard dose of insulin and not by the rate of recovery This is in keeping with Soskin's law that the amount of insulin secreted by the normal pancreas in response to ingestion of a standard dose of glucose is constant The Staub-Traugott phenomenon is due to increasing sensitivity to insulin after repeated doses of glucose

The utilization of sugar by the peripheral tissues is measured by the difference between arterial and venous blood sugar value (A–V difference) and more comprehensively by arterial venous tolerance curves The A–V difference is small in the fasting state but increases after glucose The diminished ability of the peripheral tissues to remove sugar after a low carbohydrate diet is adequately compensated for by a raised blood sugar concentrate Insulin insensitivity is determined by pituitary secretion and pituitary extracts retard oxidation of sugar and insulin action in the peripheral tissues and increase production of sugar from non carbohydrate sources by the liver both processes resulting in the maintenance of an adequate blood sugar concentrate for the particular circumstances It may be that the secretion of the pituitary diabetogenic complex is dependent upon some centre in the brain reacting sensitively to levels of blood sugar concentration in the neural fluid

Falta (1936) claimed to have differentiated clinical diabetes into two types insulin sensitive who require little insulin to prevent the excretion of many grams of urinary sugar tolerate little or no increase in insulin dosage without showing hypoglycaemic symptoms and react to withdrawal of insulin by profuse glycosuria and insulin insensitive who require many units of insulin to deal with each gramme of sugar tolerate an overdose of insulin well and on cessation of treatment show little or no glycosuria Himsworth devised the insulin glucose test which consists of the injection intravenously of a dose of insulin (5 units per square metre of body surface) and immediately afterwards giving a dose of glucose by mouth (30 gm per square metre of body surface) and estimating the blood sugar at short intervals during the hour In the insulin sensitive type the insulin acts immediately and suppresses the alimentary hyperglycaemia with insulin insensitive types the action is retarded

and inadequate If the insulin glucose curve is plotted on the same graph as the glucose tolerance curve the difference in area between the former (*I*) and the latter (*G*)—the *I*/*G* ratio—is a measure of insulin sensitivity For insulin sensitive patients the *I*/*G* ratio is approximately 1 0 or more for insulin insensitivity the *I*/*G* ratio is 0 5 or less Intermediate types may be met with The insulin sensitive type tend to be younger and thin and to have normal blood pressure and normal arteries and the disease has been sudden in onset and severe the insulin insensitive type tend to be elderly and obese and to have hypertension and arteriosclerosis the onset of the disease having been insidious The former develop ketosis easily and the latter rarely If the insulin glucose curves are carried on for 3 hours it is seen that the action of insulin in the insensitive type although considerably delayed is ultimately as cumulatively effective as in the sensitive type Insulin insensitivity is due to the pituitary factor and clinically the diabetes of acromegalics and of patients with Cushing s syndrome is often refractory to insulin a refractoriness which disappears after deep radiation of the pituitary gland The serum of insulin resistant diabetics when injected into rabbits may render them insulin insensitive but results are variable and contradictory The part played by the adrenal cortex in determining insulin insensitivity has not yet been properly elucidated but there is no doubt about its importance

(Insulin sensitivity is also measured by injecting intravenously 0 1 units of insulin per 1 g body weight in the fasting state and measuring blood sugar concentration over the next 3 hours The second half of the curve measures the rate of recovery from hypoglycaemic levels that is hypoglycaemic responsiveness or unresponsiveness which is dependent both upon pituitary and adrenal cortex factors The patient should be well fed for 3 days before the test)

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carbohydrate metabolism The anterior pituitary gland secretes a diabetogenic hormone and a suitable extract can produce and maintain a high blood sugar in the absence of all the viscera except the liver (though some experiments suggest that the adrenal cortex may al o be necessary) The anterior pituitary however also secretes a hormone which causes *hyperplasia of* the islets of Langerhans and resulting hypoglycaemia The posterior pituitary gland (pitressin) rai es the blood sugar level and will prevent or counteract insulin hypoglycaemia

An extract of the adrenal cortex (cortin) raises the blood sugar and hepatic glycogen of young rats though exercising no immediate effect in man Hyperplasia or adenoma however produces hyperglycaemic glycosuria Adrenaline raises the blood sugar being secreted in increased quantities during hypoglycaemia Both adrenaline and pitressin act quickly by mobilizing hepatic glycogen whereas the adrenal cortex and the anterior pituitary act more slowly and less obviously

The influence of the thyroid on carbohydrate metabolism is less easily demonstrated but thyroxin probably mobilizes glycogen by increasing the effects of sympathetic activity and conversely thyroidectomy (like hypophysectomy) diminishes the sensitivity of hepatic glycogen to adrenaline (see also Hypoglycaemia)

(d) Incidence

Diabetes mellitus occurs about equally in both sexes and at all ages it has been reported in infancy When occurring in successive generations the age of onset may become progressively younger It is a familial disease and is said to be a Mendelian recessive A high incidence occurs in those of Hebrew race

(e) Clinical Picture

The excess of sugar in the blood produce diuresis polyuria and polydipsia the inability to utilize sugar (storage and combustion) results in hunger polyphagia and loss of weight

Complications are boils carbuncles dermatitis prurigo pruritus ani and vulvae endarteritis with ulceration and gangrene cataract retinitis phthisis amenorrhoea and occasionally impotence and infantilism

The associated disturbance of fat metabolism leads to ketosis

B CLINICAL

CHAPTER XLVIII

DIABETES MELLITUS

(Hyperglycaemic Glycosuria)

(a) Definition

DIABETES mellitus is a condition of hyperglycaemic glycosuria due to the inadequate production or utilization of insulin or to a hyperactivity of those endocrine glands (pituitary adrenals thyroid) whose secretions normally balance or counteract the influence of insulin There is also an associated disorder of fat metabolism

(b) Historical

This disorder was known to the ancient Greeks (διαβητης siphon μελι honey) the sweet taste of the urine was rediscovered by Thomas Willis in 1674 and this was proved by Matthew Dobson to be due to sugar by evaporating the urine Dobson also detected the sweet taste of blood serum thus giving the first indication of hyperglycaemia Brunner in 1682 produced thirst and polyuria by pancreatectomy in a dog and glycosuria was shown to follow this operation by Mering and Minkowski in 1889 Hedon in 1893 first ascribed an internal secretion to the islets of Langerhans and in 1922 Banting and Best produced insulin from the pancreas Collip and Macleod making valuable contributions to this work

(c) Pathology and Physiology

The *islets* of Langerhans show hyaline degeneration and fibrosis in some instances but even when the remaining endocrine glands are apparently normal the pancreas does not necessarily show histological change Further the pancreas of a fatal case may contain a high content of insulin suggesting an *inability* to discharge or utilize insulin rather than a deficient formation

Not all forms of diabetes mellitus are of pancreatic *origin* and other endocrine glands play an equally important part in

no glycosuria or hyperglycaemia and urine of low specific gravity being controllable by injections of pitressin

Diabetic coma may be preceded by malaise headache nausea and vomiting epigastric pains and drowsiness In coma the breathing is deep and sighing the face congested the reflexes diminished or absent the patient being dehydrated with loss of tension in the eyeballs The breath smells of acetone which is present in large quantities in the urine (For differentiation see Hypoglycaemic Coma)

Haemochromatosis (*Bronzed diabetes*) which nearly always occurs in males is a metabolic disorder in which an iron pigment (haemosiderin) is deposited in the liver and pancreas &c producing a large cirrhotic liver and diabetes mellitus Pigmentation is greyish and diffuse Haemosiderin may also be deposited in the adrenals producing associated Addison s disease

Lawrence and Oakley (1947) have pointed out that the arteriosclerotic complications of diabetes mellitus are not encountered in haemochromatosis and coma is rare Bonlin (1945) recorded a series of 70 cases of haemochromatosis out of a total of 4 266 diabetics (i e 1 6 per cent) and noted that insulin requirements progressively increased together with an increasing insensitivity to insulin that 12 per cent died in diabetic coma that impotence was present in 40 per cent of the males and no less than 12 per cent showed testicular atrophy

(g) Course and Prognosis

Adequate control of the diabetes may result in improved tolerance but rarely in cure Inadequate control leads to coma in the young but older people are more likely to suffer from various complications (see above)

(h) Treatment

A low carbohydrate diet is suitable for mild cases especially in old people All children need insulin Though the apparent aim of insulin is to bring the blood sugar to normal levels it also affects the whole metabolism and abolishes or prevents complications (unfortunately it cannot prevent or influence diabetic retinitis) Some physicians keep the blood sugar constantly below 160 mg per 100 c c and even aim at securing hypoglycaemic attacks for it is urged that an improved tolerance and

and diabetic coma Blood cholesterol may be raised and lipoid deposited in the skin e g xanthomas of eyelids It is said that adiposity predisposes to the onset of diabetes in middle age Modern knowledge would rather suggest that both the adiposity and the diabetes may result from hyperactivity of the anterior pituitary

(f) Diagnosis

The older physicians diagnosed diabetes mellitus on the symptomatology and the presence of glycosuria The development of a simple technique for blood sugar determinations then led to the recognition of a characteristic diabetic curve after 50 gm of glucose (glucose tolerance test) with the blood sugar rising above 180 mg per cent and remaining high for longer than 90 minutes Lexton has drawn attention to an innocent type of hyperglycaemic glycosuria in which the blood sugar curve is identical with that of true diabetes mellitus but the patient remains free of symptoms on unlimited diet It is therefore urged that whatever the blood sugar curve diabetes mellitus should not be diagnosed readily in the absence of symptoms A further source of fallacy in blood sugar tolerance curves is the fact that reduced diet or starvation in a normal individual results in the production of a tolerance curve resembling that of a diabetic Alleged diabetics therefore should not be put on a restricted diet before testing their carbohydrate tolerance If ketone bodies are present in the urine as well as sugar diabetes mellitus is almost certain

Renal glycosuria (*Diabetes innocens*) is a condition in which an abnormally low renal threshold permits sugar to leak into the urine The blood sugar is however normal and there are no symptoms The renal threshold in true diabetes mellitus may be normal (180 mg level) high or low though varying from time to time The pregnant woman may have a low renal threshold or may excrete lactose

Diabetes mellitus may occur with acromegaly with Cushing s basophilism syndrome and with tumours or hyperplasia of the adrenal cortex A reduced carbohydrate tolerance may follow castration and the menopause

Diabetes insipidus is due to a lesion of the *hypothalamic* pituitary region and is manifested by polyuria and polydipsia

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in some cases cure will be produced only by such a regimen Hypoglycaemic attacks are however extremely disconcerting if not dangerous and physicians who do not take such a severe attitude urge that the percentage of cures is too small to justify putting their patients to such inconvenience Certainly the patients often feel much better when their blood sugar does not reach hypoglycaemic levels and a trace of glycosuria is not necessarily deserving of censure

When insulin is used it is not necessary to restrict the carbohydrate to low values such as 80 gm a day and some patients do very well on high carbohydrate diets e g carbohydrate 300 protein 80 and fat 60 gm *per diem* Their diet being more like that of an average adult is likely to be more acceptable and consequently to be adhered to

Zinc protamine insulin Ordinary insulin begins to act in 20 minutes has a maximum effect in 3 hours and has ceased to act within about 8 hours Its immediate action has obvious advantages but efforts have been made to increase the duration of its action Leyton used a suspension of insulin in castor oil Clausen added minute quantities of adrenaline to insulin to retard absorption Hagedorn succeeded in linking insulin to a natural protamine from fish sperm (insulin retard) Scott added traces of zinc to protamine insulin thus producing still slower action

This zinc protamine insulin constitutes a uniform suspension and the nature of the physico chemical union is not yet clearly defined It is on the market in concentrations of 40 units and 80 units per c c The zinc is present in only minute traces 1 mg in 500 units of insulin and no evidence of zinc poisoning has been recorded

Zinc protamine insulin begins to act 6 hours after injection has a maximum effect at 12 hours and ceases to act after some 28 hours This time relationship has the advantage of making possible the control of sugar concentration over a period of 24 hours by one instead of two or three injections

It is usually given before breakfast (but in some patients an evening injection ensures a better balance) The fact that its action may not begin for some hours means that in some cases breakfast is followed by hyperglycaemia and glycosuria To obviate this a dose of ordinary insulin may be given at the same

time For exactitude this should be given in a separate syringe but even when given in the same syringe as the zinc protamine insulin a variable but considerable proportion of the insulin retains its physico chemical freedom and rapid action In actual practice the method is often efficacious Insulin retard (Hagedorn) has a time action curve intermediate between that of ordinary insulin and zinc protamine insulin

When hypoglycaemic attacks occur with zinc protamine insulin they tend to be much more insidious in their onset and therefore less easily detected by patient or doctor further they are more prolonged and repeated administration of glucose over a number of hours may be necessary It is therefore inadvisable to begin treatment with zinc protamine insulin except under medical supervision in hospital or nursing home

Globin Insulin

This is a form of insulin prepared by combining insulin with globin a simple protein obtained from erythrocytes by removing the non containing chromogen fraction (Reiner Searle and Lang 1939) It is also combined with zinc A solution of globin insulin is clear and colourless Its action is intermediate between that of simple insulin and zinc protamine insulin but approximates more closely to the latter Like the latter it can be used in conjunction with simple insulin Its duration of action is nearer 20 hours than the 28 hours of zinc protamine insulin It is therefore less cumulative Di insulin is a stable mixture of simple insulin and phenyl ureido insulin a single injection of which is effective for 16–24 hours Hallas Møller and Hey (1944) Slessor and Nicol (1947)

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sweating anxiety apprehension and a sense of constriction of the chest with difficult breathing (often as slow as Cheyne Stokes s but sometimes shallow and rapid) Irritability anger emotionalism inability to concentrate and insomnia may also be due to hyperadrenalism The pupils are dilated

(f) Cerebral Manifestations

(i) Motor inco ordination of hands and legs ataxia tran sient hemiplegia or monoplegia convulsions (especially in children) and coma Attacks of *petit mal* and *grand mal* may occur and rigid flexion of arms

(ii) *Sensory* Numbness and tingling sensations Headaches may be severe and migrainous in nature

(iii) *Ocular* Diplopia blurred vision dilated pupils unequal pupils and nystagmoid movements may be features

(iv) *Disorders of behaviour* The patient may exhibit degrees of mental confusion acting in a purposeless fashion A child may climb a drinking fountain or carry out swimming move ments on the grass or rub his head on the nurse s arm Memory may be impaired complete amnesia of the hypoglycaemic period being quite common Various forms of neurasthenia and psycho neuroses have been associated with hypoglycaemia hallucina tions and delusions also occur

(v) *Gastro intestinal* Hunger is a common feature the patient being at times ravenous The degree of shock however may be too severe for hunger to be noticed or expressed There is evidence that hypoglycaemia stimulates the vagus nucleus to produce gastric hypermotility and hyperacidity followed by hunger and sometimes severe abdominal pain (Possibly this is the physiological mechanism underlying appetite)

(vi) *Other symptoms* Aphasia is not infrequent the patient being unable to think of the right word or muddling the con struction of a sentence Yawning or purposeless smacking of the lips may be features salivation is sometimes profuse

(vii) *Adiposity* The more chronic cases usually become fat partly from frequent carbohydrate meals necessary to combat the hypoglycaemia and increased appetite But insulin must act more directly on fat metabolism e g the fatness of some diabetic children after administration of insulin is sufficient to suggest Frolich s syndrome

(g) Diagnosis

Severe hyperinsulinism produces a clinical picture characterized by severe shock as described above But though the indications of hypoglycaemia may be incomplete and relatively slight it is particularly important for the psychiatrist and neurologist to remember its possibility especially in petit mal grand mal loss of memory the psychoneuroses and inexplicable disorders of conduct Convulsions in infancy and childhood may be caused by hypoglycaemia sometimes from a physiological stimulus

Low fasting blood sugar and the relief of symptoms by intravenous glucose confirm the diagnosis of hypoglycaemia With pancreatic islet cell neoplasm or hyperplasia the usual oral glucose tolerance test may be normal but hypoglycaemia is met with after 3 or 4 hours The intravenous glucose tolerance test is always followed by hypoglycaemia The insulin sensitivity test is normal in functional hyperinsulinism but shows hypoglycaemic unresponsiveness in organic hyperinsulinism (Luft 1947)

The differential diagnosis from diabetic coma may be important In diabetic coma the face is flushed and congested the respiration deep and sighing the reflexes diminished or absent and the plantar reflexes flexor In hypoglycaemic coma the face is pallid the respirations may be shallow but are sometimes slow and deep the reflexes often increased with some spasticity of the limbs (until the terminal flaccidity sets in) and the plantar reflex extensor The temperature in hypoglycaemic coma is subnormal but in diabetic coma it may be normal or raised The urine in hypoglycaemia is free from sugar and acetone

(h) Treatment

The immediate treatment of hypoglycaemia is the administration of sugar by mouth or by nasal or stomach tube or intravenously If the condition is not due to an hepatic lesion the injection of 1 c c of adrenaline may restore consciousness

But determination of the underlying pathology is of course fundamental should the condition be chronic and recurrent abdominal laparotomy may be called for in the absence of an obvious lesion of the adrenals pituitary or thyroid If a

pancreatic adenoma is found (sometimes two may be present) it should be removed and cure will result. A partial resection should still be undertaken if the pancreas is apparently normal and, even when the histological appearance of the excised pancreas appeared to be normal, cure has resulted. A carcinoma of the pancreas may be the source of metastases to the liver, &c.

If surgery is refused, medical treatment consists of frequent meals at short intervals. Sometimes small doses of insulin given after meals are effective. Presumably they act by preventing a hyperglycaemia which would have stimulated the pancreas to insulin production.

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APPENDIX

I PRESCRIBING AND STANDARDIZATION OF HORMONES

IN the previous edition of this book a comprehensive list of proprietary preparations was given although the writer deplored the confusion of names of no scientific significance The work of the Medical Research Council in obtaining universally accepted gravimetric standards for most hormones based on a given weight of isolated (or purified) hormone including even powdered forms of gonadotrophic hormone makes it unjustifiable to continue all these trade names and wherever possible gravimetric units should replace the more variable biological standardization It is therefore proposed that scientific names be used and the dose prescribed wherever possible in milligram The option of adding the name of a reliable firm of manufacturers in parenthesis is naturally left to the individual prescriber s whim or judgement

		Tablets (Oral)	Injections
OESTROGENIC HORMONES			
Oestradiol benzoate	1 to 5 mg	Yes	Yes
Oestrone	0 1 0 3 1 0 mg	Yes	No
Stilboestrol	0 5 to 5 mg	Yes	Yes
Hexoestrol	0 5 to 5 mg	Yes	Yes
Dienoestrol	0 1 to 5 mg	Yes	Yes
PROGESTATIONAL HORMONES			
Progesterone	5 to 10 mg	No	Yes
Ethisterone (anhydro hydroxy progesterone)	5 to 10 mg	Yes	No
GONADOTROPHIC HORMONES			
Serum gonadotrophin (from cattle)	500 to 1 000 biological units	No	Yes
Chorionic gonadotrophin (from human pregnancy urine)	500 to 1 000 biological units	No	Yes
Pituitary gonadotrophic	See individual trade preparations which often contain chorionic gonadotrophins as well e g Synapoidin (P D & Co) Ambinon A (Organon)		

(N B The international standard for chorionic gonadotrophin is 0 1 mg (= 100 gamma) The gravimetric unit happens to correspond to

an amount of activity very similar to that required to cause cornification of the vaginal epithelium of the immature rat (1 rat unit) A similar standard of 0 1 mg for serum gonadotrophin gives a less constant biological equivalent)

ANDROGENIC HORMONES

		Tablets (Oral)	Injections
Testosterone propionate	10 25 50 mg	No	Yes
Methyl testosterone	5 mg	Yes	No

ADRENAL CORTEX

A Desoxycorticosterone propionate	5 mg	No	Yes
B Corticosterone group	Not available		

Some aqueous extracts containing A and B are
Eucortone (A & H) Eschatin (P D & Co)

Suggested name Cortical Extract	5 to 20 c c	No	Yes

(Eucortone and Eschatin &c are made from the adrenal glands of cattle An Upjohn preparation called Lipo Adrenal cortex made from pigs adrenals is available in America as a concentrated extract containing a high production of glycogen steroids (corticosterone group)

PITUITARY CORTICOTROPHIC HORMONE

Pituitary corticotrophic hormone	100 units per c c	No	Yes

PITUITARY THYROTROPHIC HORMONE

Pituitary thyrotrophic hormone (Organon)—for experimental and diagnostic purposes

PITUITARY GROWTH HORMONE

Pituitary growth hormone (Armour s P D & Co)	100 units per c c	No	Yes

PITUITARY LACTOGENIC HORMONE

Pituitary lactogenic hormone	60 Riddle units per c c	No	Yes

II THE APPFARANCFS OF OSSIFIC CENTRES AS AN INDEX OF SKELETAI DEVELOPMENT (BONE AGE)

By A M RACKOW D M R E

Ral ol gist to P in es Lo se Cl ldren s Un t

DURING the first f years of lif the X ray appearance of the wrist forms the most useful criterion of bone ag The order of appearance of the ossific centres for the carpal bones remains onstant but the times at which the centres become radiologically apparent may differ a little in the comparison of normal individuals

The diagram in Fig 78 is presented as a reminder of the di tribution of the centres in the carpus there being one centre for each carpal bone

Up to 3 months after birth, no ossific centre may be visibl in the carpus (Fig 79)

Between 3 months and 12 months of age centres for the os magnum (os capitatum) and unciform (os hamatum) appear in that order (Fig 80)

Between 1 and 3 years of age an additional centre for the cuneiform (triquetrum) becomes visible (Fig 81)

Between the ages of 3 and 5 years the two c ntres for the semi lunar (os lunatum) and trapezoid (os multangulum minus) appear in that order (Fig 82)

At 6 years of age centres for the scaphoid (os naviculare manus) and trapezium (os maltangulum majus) appear and all the carpal bones with the exception of the pi iform which ossifies at 10 years should be visible (Fig 83)

When the child is in the vicinity of the 10th year a lateral view of the elbow provid s a useful bony landmark since in the 10th year the epiphysis of the olecranon process should be appearing Sometimes thi centre is double (Fig 84)

One returns to the wrist after puberty when seeking evidence of precocious or delayed bony development since fusion of the epiphyses of the lower end of the radius and ulnar with their re pective shafts should take place betwe n the ages of 16 and 18 (Fig 85)

Supplementary evidence (femur)

At certain ages the state of the upper end of the femur may be a useful additional guide to bony development

During the first decade an X ray of the hip joint with the leg held in external rotation should show

At 1 'th month	the osseous centre for the head
In the 4th year	the osseous centre for the great r tro hanter



Fig 79 At 3 months



Fig 80 At 1 year

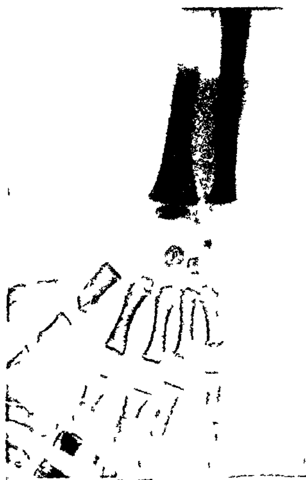


Fig 81 At 1½ years

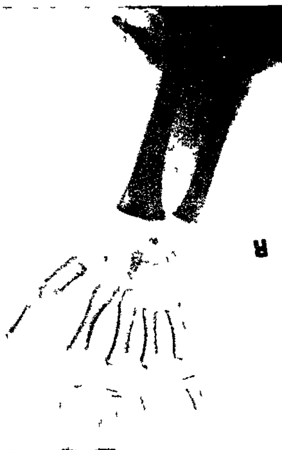


Fig 87 At 4½ years



Fig 83 At 6 years



Fig 84 At 10 years



FIG 83 At 6 years



Fig 86 Male aged 14 Head unfused

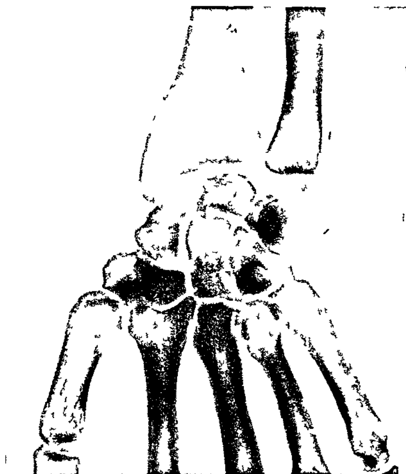


Fig 85 At 17 years



FIG 88 Female aged 14 Head unfused



Fig 87 Male aged 16 Head partially fused



Fig. 88 Female aged 14 Head unfused



Fig 89 Female aged 16 Head fused

INDEX



Fig 89 Female aged 16 Head fused

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